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DETERMINANTS OF DRUG UTILISATION DURING CHILDHOOD

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ABSTRACT

Paediatric pharmacology is a neglected area in terms of rational use of drugs. Wide differences have been observed in children's exposure to drugs between and within countries and regions. The aim of the current thesis is to investigate the determinants of drug prescription in paediatrics. Pharmacoepidemiology and the use of administrative databases can be a useful tool for this scope.

Data collected in regional and multiregional administrative prescription databases were analysed. Prevalence data by sex and age were calculated by dividing the number of drug users by the total number of male and female residents in each age group. Univariable and multivariable analyses were performed with the aim to identify the determinants of drug prescriptions.

The studies showed quantitative and qualitative differences in drug prescription to children and adolescents among Italian regions and within regions. The prescription of a great number of different, redundant, active substances, even among experienced paediatricians, was found. A North-South trend was found in antiasthmatic and antibiotic prevalence, with an important association with average income at the area level. A confirmation of the high prevalence of these drugs and poor qualitative profile was also found.

Large heterogeneity was found in psychotropic drug prevalence among different Italian regions. Psychotropic drugs were scantily prescribed and some of the most used drugs were prescribed off-label. The analyses of the prescription of generic antibiotics showed that generic formulations are scantily prescribed by Italian paediatricians, and the lowest prescription rate of generic drugs was found in paediatricians who prescribe more antibiotics. Some quality indicators for antibiotic prescribing were developed at the paediatrician level. The youngest paediatricians and those who were not exposed to educational interventions showed a significantly worse quality of prescribing. The thesis provide some useful data for policy makers in order to improve the rational drug use in children.

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PUBLICATIONS AND PRESENTATIONS RELATED TO THIS THESIS

Published Papers:

- Piovani D, Clavenna A, Cartabia M, Bonati M. Antibiotic and anti-asthmatic drug prescriptions in Italy: geographic patterns and socio-economic determinants at the district level. *Eur J Clin Pharmacol*. 2014; 70:331-7.
- Piovani D, Clavenna A, Cartabia M, Bonati M. Psychotropic medicine prescriptions in Italian youths: a multiregional study. *Eur Child Adolesc Psychiatry*. 2016; 25:235-45.
- Piovani D, Clavenna A, Bonati M; PeFAB group. Review of Italian primary care paediatricians identifies 38 commonly prescribed drugs for children. *Acta Paediatr*. 2014; 103:e532-7. doi: 10.1111/apa.12783.
- Piovani D, Clavenna A, Cartabia M, Bortolotti A, Fortino I, Merlino L, Bonati M. Comparing recurrent antibiotic prescriptions in children treated with a brand name or a generic formulation. *Pharmacoepidemiol Drug Saf*. 2015; 24:121-8.
- Piovani D, Clavenna A, Cartabia M, Bortolotti A, Fortino I, Merlino L, Bonati M. Assessing the quality of paediatric antibiotic prescribing by community paediatricians: a database analysis of prescribing in Lombardy. *BMJ Paediatrics Open* 2017; 1:e000169. doi: 10.1136/bmjpo-2017-000169

Published Abstracts:

- Drug prescription profile and perinatal determinants during the first year of life. *Arch Dis Child* 2016;101:e1 doi: 10.1136/archdischild-2015-310148.3 15° Biannual Congress of the European Society for Developmental Perinatal Paediatric Pharmacology (ESDPPP), Belgrade, Serbia, 23-26 June 2015.

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LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
ASST	Azienda Socio-Sanitaria Territoriale (social health territorial unit)
ATS	Azienda di Tutela della Salute (health protection territorial agency)
AUC	Area Under Curve
CV	Coefficient of variation
EMA	European Medicines Agency
EMLC	Essential Medicines List for Children
FP	Family Paediatrician
GP	General Practitioner
ICD-9	International Classification of Diseases, 9th Revision
INN	International Non-proprietary Name
LHU	Local Health Unit
NICE	National Institute for health and Care Excellence
NHS	National Health Service
NPF	National Pharmaceutical Formulary
RADT	Rapid Antigen Detection Test
RCT	Randomised Controlled Trial
RTI	Respiratory tract infections
SD	Standard Deviation
SSRI	Selective Serotonin Re-uptake Inhibitors
URTI	Upper respiratory tract infections

I. Introduction

1. Background

Improving the rational use of drugs and the use of health care resources are important research topics in the public health field, even in western countries [1]. The World Health Organization estimated that half of the prescriptions filled worldwide are inappropriate [2]. Children are among the most exposed to drugs, with an estimated prevalence of 60% in western countries [3]. This population of patients is also inherently one of the most fragile, hence inappropriate treatments should be avoided as much as possible.

In the literature, qualitative and quantitative differences have been found in the prescription of drugs to children between and within countries, and even in the same regions, showing that patterns of use are largely heterogeneous even within the same geographic setting [3-6]. According to available data, the prescription rates of drugs in children in western countries range from 0.8 in Norway (1988-89) to 3.2 prescriptions per child in USA (1992-93) with large heterogeneity also in the methodological aspect of studies[3]. Large differences in antibiotic exposure (the most used drug class among children) between countries have been found. An Italian child has, on average, a fourfold higher risk of being exposed to antibacterial drugs than an English child and a threefold higher risk than a Dutch child, with increased prescription rate of second choice antibiotics [4]. Wide differences have been observed also in children's exposure to anti-asthmatics between different countries: prevalence ranges from 6.2% in Norway to 19% in Italy [5].

The heterogeneity found, however, does not seem to be related to differences in disease epidemiology but, in most cases, to inappropriate use [7,8]. For example, cephalosporins, a second line treatment in most paediatric infections, are widely prescribed in Italy, while in the Netherlands and Denmark this class is hardly prescribed [4]. Also, in Italy, the use of inhaled steroids, such as beclometasone, is threefold and fourfold higher than in UK and in the Netherlands, respectively, because such treatments are prescribed in nebulised formulations in Italy mainly as symptomatic treatment of upper respiratory tract infections (URTI) [5, 9-11].

The determinants of inappropriate use or over-prescription are many and complex. Some have been studied in depth, such as the FP's attitude to prescription [12]. The most important factors linked to the family paediatricians' (FP) over-prescription are diagnostic uncertainty and perceived parental expectations of a prescription [13]. The existing healthcare system and patient- or parent-related sociocultural and economic determinants may also, however, be responsible for geographic differences in prescription profiles [14]. These associations have been described, but have been studied to a limited extent. For example, there is recent evidence that children receiving a high quantity of antibiotics belong to families that use more drugs in general [15]. Another study found that children receiving a psychotropic drug had a higher chance of having a family member with a psychiatric disorder [16]. There is evidence that children receiving hypnotic prescriptions were more likely to have mothers who receive hypnotic prescriptions themselves, implicating that mothers were able to somehow influence the prescribing process [17]. It is not, however, understood how the socio-cultural and health status of the families can influence drug use in children.

The use of healthcare databases to conduct retrospective studies is an important research tool concerning drug and health resources use. In fact data linkage of healthcare databases permits the assessment of large populations, it is flexible in design, has high speed of use, and avoid issues such as selection biases that are typical of other investigation tools like surveys or non-randomized *ad hoc* studies [18]. The use of real world-data that are routinely collected during the course of health care delivery can be a cost saver in respect to large RCTs for answering relevant epidemiological questions [19]. The important limitations of the healthcare databases available for use in this thesis will be discussed in the Methods section.

2. Previous drug utilisation studies at our laboratory

In the past years the Laboratory for Mother and Child Health have produced a number of studies concerning drug utilisation, including reviews of the literature, and studies on the rational use of drugs in paediatrics. In this section I will summarize some of the main findings that are relevant to this thesis.

a. Studies concerning any drug

A review of the literature found that the prevalence of any kind of drugs in paediatrics ranged between 51% in Denmark to 70% in Greenland and the prescription rate ranged from 0.8 in Norway to 3.2 prescriptions per person in the United States [3]. The review also found large heterogeneity in the methodological quality and outcomes reported.

A study investigated the drug prescription profile in the Lombardy Region and found a prevalence ranging between 38.4 and 54.8%. Drug prevalence was not correlated to hospitalization rate in the paediatric population. Being younger (1-5 years old), and living in the eastern part of the region were the factors associated with the highest risk of drug exposure [20].

A more recent study investigated the prevalence of drug prescription in three Italian regions finding large differences among Local Health Units – LHUs - (ranging from 43.1% to 70.0%), with an increased chance to receive a prescription in the South of the country [8]. Finally, a study investigated the differences in prescribing between GPs and FPs finding that children cared for by GPs had an higher chance to receive any drugs compared to those cared for by FPs [21].

b. Studies concerning antibiotics

A review of the literature found quantitative and qualitative differences in the antibiotic prescription profile between and within countries. Moreover, differences were found also at the local level and between prescribers. In general, second-choice antibiotic drugs were more commonly prescribed in settings characterised by a high prevalence of antibiotic prescription [4].

A study on seven Italian regions found that prevalence ranged from 42.6% to 62.1% among regions, and at the LHU level they ranged from 35.6% to 68.5%. There was a trend indicating that in southern regions antibiotics were more frequently prescribed than in the northern and central regions. Overall, penicillin covered 53.1% of antibiotic prescriptions, with differences between regions ranging from 39.2% to 62.5% with a North-South trend [6].

Another study on the Lombardy Region (the region with the highest population density in Italy, accounting for 1/6 of the Italian population) compared the prescription profile of a group of FPs that has been involved in initiatives concerning care for years with that of the others FPs in the region [22]. The study found a better qualitative profile in the FPs involved in educational initiatives. The study also found that by improving prescribing appropriateness (i.e. by increasing amoxicillin prescription), it would have been possible to reduce the expenditure associated with antibiotic prescriptions to outpatient children by about one-fifth [22].

c. Studies concerning antiasthmatics

A review of the literature found that the overall prevalence of antiasthmatics was 13.3%, and wide differences were found between countries, ranging from 6.2% in The Netherlands

to 19.0% in Italy [5]. The review found an heterogeneous quality of the studies in respect to the outcome measures reported [5].

A study on an Italian LHM found a prevalence of 12%, with high proportion of users being occasional (58%). The study found that the prevalence of anti-asthmatic prescription was much higher than prevalence of disease, indicating that anti-asthmatics were over-prescribed. High use of nebulized steroids, mainly prescribed only once in a year, was found, supporting the hypothesis that they were prescribed not for asthma but as a symptomatic treatment of URTIs [23]. The study recently prompted a RCT on the effectiveness of nebulised beclomethasone in preventing viral wheezing [24]. The study showed that nebulised beclomethasone is not effective in preventing recurrence of viral wheezing, nor in reducing symptoms of respiratory tract infections, showing that its use for these indications is not evidence-based [24].

Most of the antiasthmatics prescribed in Italy are not used for asthma but for the treatment of symptoms of common URTI without robust evidence of efficacy. Thus, a method of assessing asthma prevalence in a children population starting from prescription data was validated in a more recent study, by considering only pressurised formulations of antiasthmatics [25].

d. Studies concerning psychotropic drugs

A review of the literature found an increase in psychotropic drugs among paediatric patients in different countries in the past decade [26]. This increase was especially evident for stimulants and selective serotonin reuptake inhibitors. The analysis of the epidemiological data suggested that the risk of inappropriate use or abuse of these drugs was high [26].

A study conducted in a LHU of the Veneto Region showed that the prevalence of prescription of psychotropic drugs was low in the 2004-2008 period compared to other countries, and the incidence slightly increased from 7.0 in 2005 to 8.3 per 10,000 children in 2008 [16]. Despite the low prevalence, most children receiving a pharmacological treatment were not cared for by child and adolescent psychiatric services [16].

A successive study in the Lombardy Region found that 59,987 youths (37.1‰) attended a child and adolescent neuropsychiatry service at least once, but only 2,761 (1.7 ‰) received a pharmacological treatment, confirming the low use of psychotropic drugs compared to other countries [27]. Also in this study 57% of the youths who received a pharmacological treatment did not attend a child neuropsychiatry service [27].

3. Summary of the thesis

This thesis is an attempt to evaluate the determinants of drug prescription in children in more detail.

For doing so, the first part of the thesis is aimed at exploring the literature concerning the association between parents and child drug prescription and/or use. The aim of this review was to focus on a neglected area in terms of determinants of drug use, and this is an area that is potentially important but that was not investigated before in my laboratory. A systematic review of the literature was performed with the aim to collect the studies and the results of epidemiological studies that used administrative databases that evaluated the association between drug use or prescription in parents and their offspring.

The rest of the thesis focuses on studies performed using administrative databases. The first part focuses on some determinants of antibiotic, antiasthmatics, and psychotropic medicine prescriptions in large multiregional studies, which involved up to half of the children and adolescents Italian population, and are quite representative of the different

socio-cultural and geographical heterogeneity. In this first part the determinants of the prevalence of prescription of this drug classes was evaluated in respect to the geographical and income factors.

In the last part of the thesis an evaluation on the quality of drug prescription and on the associated determinants, was performed with three studies. The first study was performed in collaboration with a group of experienced FPs involved in educational activities since 2004. We collected information about the overall drug prescribed by this group in two consecutive months, and estimated a list of the most commonly prescribed “essential” drugs in the context of daily clinical practice in Italy. The other three studies employed the Lombardy Region administrative databases, the first study regarded the prescription of generic and brand name formulations of antibiotic in the clinical practice. The high prescribing paediatricians were found more likely to prescribe a brand name antibiotic than the low prescribing colleagues.

In the second study proxy of safety and effectiveness were evaluated for the brand name and generic antibiotic, finding no differences both in the rate of recurrent prescription following a brand name versus generic prescription, and in the rate of hospital admissions.

Finally the last study evaluated the quality of FPs’ antibiotic prescriptions by testing two newly identified indicators of quality of prescribing at the FP level. These indicators were elaborated starting from the epidemiology of the infectious diseases and some epidemiological data concerning the reasons for access to ambulatory care for the most common bacterial RTI in the Lombardy Region. The determinants of the quality of antibiotic prescribing was investigated in respect to a number of FP characteristics such as sex, age, number of patients, geographical factor, being an high or low prescriber.

II. Aims

The main aims of the project were:

1. To evaluate the determinants of drug prescriptions in a large Italian out-patient paediatric population by using administrative databases.
2. To compare the prescribing patterns in different settings, at different levels (national, regional, local)
3. To monitor drug prescription patterns and the quality of therapies by evaluating their adherence to international treatment guidelines
4. To estimate the quality of drug prescription in different settings, and in respect to different topics, including the prescription of generic antibiotics versus brand name drugs.

III. Methods

A. Pharmacoepidemiology

Pharmacoepidemiology is defined as the study of the use and effects/side-effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective use of drugs in the population and thereby improving health outcomes [28]. Pharmacoepidemiology is strictly associated with large health care databases, and big data are often used to address research questions within pharmacoepidemiology. In fact this discipline was born in 1960s together with the availability of large healthcare databases.

Pharmacoepidemiology, with appropriate methodologies, can be a useful tool for improving the effectiveness and efficiency of healthcare interventions [28,29]. Such improvements may be of particular relevance in the paediatric population, since limited information on the safety and efficacy of drugs used in paediatrics still exists, despite the regulatory effort at the European and global levels [30-33]. Drug utilization studies in children may be used to identify the major therapeutic problems in this population. Moreover, although rational drug therapy is important for all individuals being treated with drugs, it is of paramount importance for children.

B. Databases for healthcare research

While administrative data are not designed for research, have limitations, are often difficult to access, and the linkage required between certain databases may be unfeasible, yet they retain a great research potential. The Administrative Data Taskforce identified the following items of value associated with the use of administrative data [34,35]:

- The data already exist. There are no additional data collection costs associated with research use;
- The data are typically large datasets, permitting more detailed research to be undertaken than would otherwise be the case;
- The data records a process, which can be documented and understood;

- Linkage between data relating to different time periods can create longitudinal resources; and
- Linkage to other data sources (e.g. surveys) can enhance these resources.

Additionally health databases can provide data on diagnosed diseases through hospital admission and surgical procedures codes. The information on prescribed drugs, with appropriate techniques and integrations, can be used to estimate the prevalence of certain diseases, also in the outpatients [36].

C. The Italian NHS

Italian healthcare is provided free or at a nominal charge through a network of 20 Regions and 101 LHUs (on 7 March 2017). Every Italian resident is registered with a family (paediatric or general) practitioner. Children are assigned to a FP until they are 6 years old; afterwards, the parents can choose to register a child with a GP. At 14 years old all adolescents are assigned to a GP. In Italy a national formulary is available, in which drugs are categorised into three classes: class A includes essential drugs that patients do not have to pay for, class C contains drugs not covered by the NHS, class H contains drugs administered only to inpatients that are fully reimbursed, and OTC drugs. Italian outpatients receive class A prescriptions from FPs, GPs, or other specialists and then get the medicines free of charge from retail pharmacies. Outpatients receiving prescriptions in community pharmacies and get the medicines free of charge through their GP prescriptions, or their FP prescriptions if they are children. Each local pharmacy provides these prescriptions to the Regional Health Authority to get reimbursed. The majority of drugs marketed for serious conditions are fully or partly reimbursed with only a few exceptions.

A class A drug need to be prescribed by a GP or FP using a dedicated form to be reimbursed by the NHS. A specialist such as a neurologist or otorhinolaryngologist, does not necessarily use the NHS form when prescribing reimbursable class A drugs. Moreover, the NHS form

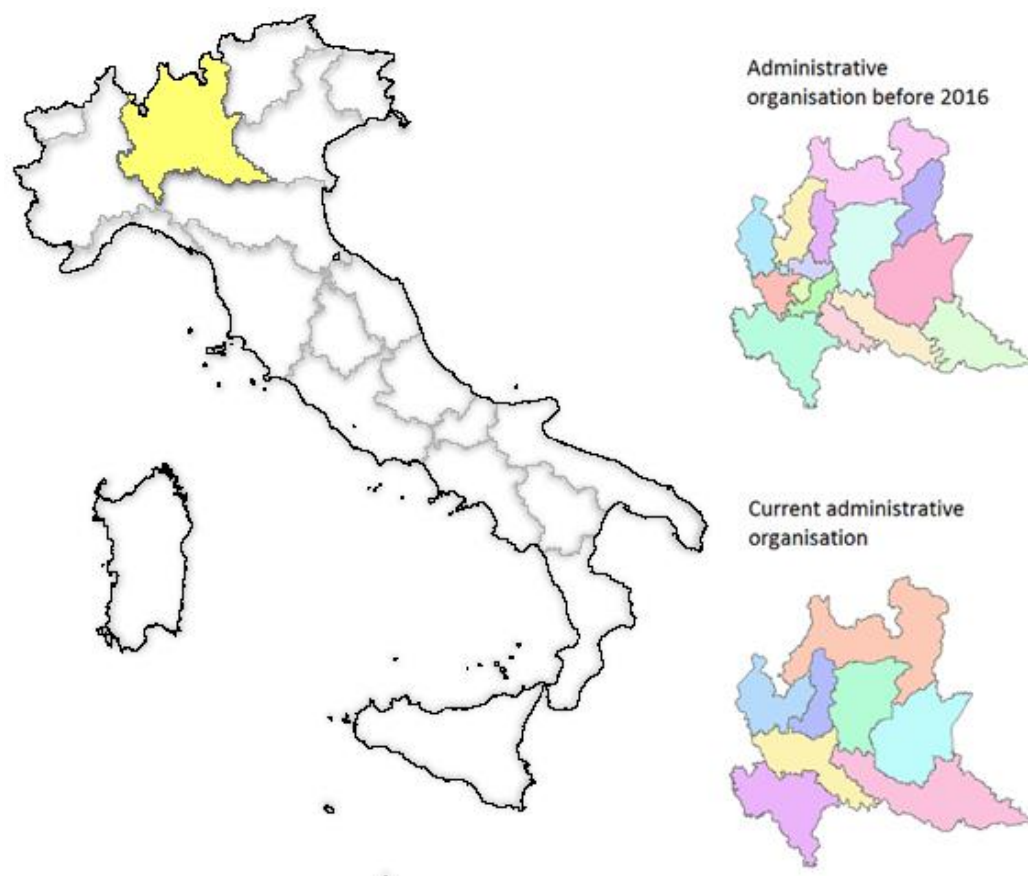
cannot be used for private visits. After a visit by a specialist, parents therefore go to their FP to obtain reimbursable prescriptions.

D. The Lombardy Region

The Lombardy Region is a large Italian region in the North of the country accounting for 1/6 of the Italian population, with a total of 1,676,730 (2017) resident children and adolescents. The region was composed of 15 LHUs and 95 healthcare districts until the reorganisation in 2016, when the LHUs were reduced to 8 (called ATS), and the healthcare districts to 27 (called ASST), figure 1. The region is among the most wealthy in Italy, and it has an heterogeneous geography, with a large plain area in the central and southern part, and mountains in the northern part. The region is very densely abitated and mostly composed of urban areas, with few rural areas.

Almost all the studies presented in this thesis used the old administrative organisation, only the last study at chapter VI.D used the new one.

Figure 1 - Lombardy Region's geographical location and administrative organisation



E. Healthcare databases

1. Reimbursed prescription database

The database contains reimbursable prescriptions (class A) routinely acquired for administrative and reimbursement reasons in the Lombardy Region. The database stores all community (i.e. outside hospital) prescriptions issued to individuals living in Lombardy Region. Within this system, a unique patient code prevents double counting of individuals who have been prescribed drugs by more than one physician. Each prescription is associated with a unique code identifying the medicine prescribed (including dosage and formulation). Other information available are: the prescription date, the number of boxes prescribed, and the prescriber and his/her characteristics.

2. Hospital discharge form database

Besides prescription data, this database contains the hospital admissions of patients classified according to the ICD-9 system [37]. The relevant information available are concerning the patients' vital statistics (age, sex, and address of residence); characteristics of the hospital stay (institute, ward and unit, type of admission, length of stay, priority) and clinical characteristics (primary diagnosis, other secondary diagnoses, diagnostic and therapeutic procedures, date of admission, discharge, or in-hospital death). Drugs administered during the hospital stay are not included in this database. Secondary diagnoses are up to to five co-existing conditions that may or may not be pre-existent.

3. Specialist visits database

Information about the outpatient specialist visits, in particular prescriptions for diagnostic tests, specialist visits, and rehabilitation performed in outpatient ambulatories are recorded for each resident patient.

Since these three databases share the same unique patient identifier - through the Patient Record Database (which contains each patient's vital statistics) - prescriptions, hospital admissions and specialist visits can be linked straightforwardly. The three databases are provided to our laboratory (Laboratory for Mother and Child Health) within the EPIFARM project, a pharmacoepidemiological project running since 2003 in agreement with the Regional Health Ministry of the Lombardy Region. Data are available for these databases since 2000. The quality and accuracy of data is routinely checked and validated each year ensuring high standards, in particular more than 99% of the patients' records were able to be linked among the three databases in 2011. Anonymity of each patient is granted by a third party society, that is not involved in any way in the analyses of the data, and that provide the laboratory with the data already encrypted within the unique patient identifier.

The other regions participating in the studies A and B, chapter V have a very similar structure of regional databases.

F. Strength and limitations of these databases and available data

The main advantage of monitoring the prescriptions dispensed by all the physicians to an entire population in a specific region. Because of the universal coverage of Italian NHS, there are not bias for the exclusion of children with different familiar socio-economic status, or concerning the prescription of more costly drugs, like it is the case in other countries. Moreover, data are available for a long time period, and this allow longitudinal studies in paediatric patients.

The main limits are that private practice physicians, over-the-counter drugs, and drugs not reimbursed by the NHS are not included. However private practice drug prescription are quite limited. Among the most important paediatric drugs that are not recorded in the database there are paracetamol, ibuprofen, antiemetic drugs and most dermatologic drugs. Other limitations are that the therapeutic indication is lacking, and that it is not possible to know if the patient actually took the drug. Moreover, information concerning the socio-economic status or the educational level of the individuals are not available. In order to overcome this issue, in some of the studies, average annual income at the area level was used as a proxy to the socio-economic status of individuals and families.

In large databases very small differences between groups can result in statistically significant differences which are not clinically meaningful. Also, even if data quality is routinely checked in terms of matching among different databases, there are possible missings or incomplete data in some of the variables which need to be checked for each study. The eventual exclusion of some of the patients for missing variables needs to be evaluated in order to check if a selection bias is likely to occur for each study.

G. Synopsis of the characteristics of the studies

Observation period and the study population varied depending on the different studies.

Table 1 summarises the main indicators (source, age group, sample size) of the studies presented in this thesis.

Table 1 - Characteristics of the pharmacoepidemiologic studies presented in the thesis

Chapter	Drug	Year	Source	Age (ys)	Sample size
V.A	antibiotics and antiasthmatics	2008	Lombardy, Lazio, Puglia	<18	1,861,425
V.B	psychotropic drugs	2007-2011	Veneto, Lombardy, Friuli Venezia Giulia, Emilia Romagna, Abruzzo, Lazio, Puglia	<18	5,019,564
VI.A	all	2012	Lombardy	<14	64 FPs
VI.B	antibiotics	2008	Lombardy	<13	1,276,932
VI.C	antibiotics	2010	Lombardy	<18	1,669,856
VI.D	antibiotics	2011	Lombardy	<14	1,164 FPs and 424,280 children

Differences in the sample chosen were due to different reasons, in part contingent (e.g. the availability of the data during the PhD project period), and in part due to the pattern of drug use. For example, in evaluating the pattern of anti-asthmatic or psychotropic drug prescriptions adolescents should also have been included, also in the case of studies that focused on FPs only children less than 14 years old where considered.

The most recent available data were analysed when performing each study.

H. Identification of drug prescriptions and patients

Prescribed drugs were classified according to the International Anatomic-Therapeutical-Classification system (ATC), which identifies the active substances. The formulations and dosage of the different active substances were identified through a univocal nine digits

code (MINSAN code). Patients were identified by using the anonymous patient identifier previously described, which prevents double counting of individuals who have been prescribed drugs by more than one physician

I. Definitions and endpoints

Proportion: the ratio of a specific quantity to the whole. Can be expressed as a percentage (i.e. the proportion of patients treated with a drug on the overall sample)

Ratio: a relationship between two quantities indicating how many times the first contains the second

Rate: the ratio between two related quantities (speed is a rate i.e number of meters per seconds), in epidemiology for example the number of prescriptions per year is a rate, and it is usually expressed per patient or per 100, 1000 patients.

When referring to prevalence in this thesis the measure to be considered is period prevalence (annual prevalence), calculated by sex and age by dividing the number of drug users by the total number of male and female residents in each age group. A person receiving at least one drug in a year is defined drug user. Point prevalence is the proportion of persons with a particular attribute on a particular date, and will not be used in this thesis. Incidence is defined as the proportion of persons receiving a prescription (new cases) in a certain period of time (usually at least one year) considering the population initially at risk. In order to evaluate pharmaceutical consumption, the number of packages of medications (cartons) was used as an indicator of the whole drug exposure during the considered period. In fact, it can be related to the same medicine prescribed repeatedly or to different medicines. The rate of hospitalisation was estimated considering hospital discharge forms, by dividing the number of patients <18 years old hospitalised at least once during the observation period by the total number of residents < 18 years old.

L. Statistical analyses

Arithmetic mean and standard deviation or, when appropriate, medians and interquartile ranges, was used to summarise continuous variables, and the t test and Wilcoxon signed-

rank tests to make comparisons among two samples. χ^2 and χ^2 for trend were used as appropriate for univariable comparisons of dichotomous data. Multivariable logistic regression was used in order to estimate risk factors increasing the probability of a given outcome.

More details concerning the statistical analyses are provided in each chapter. The results of the statistical analysis are reported in this manner: test used; degree of freedom (d.f.); p-value.

Statistical analysis was performed using SAS software, version 9.2 to 9.5, and the cartographic representations and spatial analyses with ArcMap 10.5.

A P value < 0.05 was considered statistically significant.

IV. Review of the literature

A. Drug use or prescription in parents and offsprings: a review of the literature

1. Introduction

A study on 50 families in 1980 published on the BMJ showed that children of mothers classed as high psychotropic users received twice as many antibiotics as the children of the mothers who had received no psychotropic medication [38].

A few recent studies showed that one of the possible determinants of drug prescription in children may be the amounts of drug used within his or her family [15,17]. A study in our laboratory previously showed that a child receiving a psychotropic drug had an higher chance of having a family member with a psychiatric disorder [16], indicating that prevalence of severe psychiatric disorders may be higher among youths whose parents have these disorders. Nevertheless, one of the two studies showed that a number of different drug classes were more used in parents of children receiving more antibiotics, without an apparent reason [15]. The authors hypothesised that, besides an inherited higher chance of developing a disease, parents' medicine use may influence that of children medicine prescription or use in other ways.

In order to verify if other studies found that parent's medicine use may influence that of children, and which type of drugs have been studied, I performed a systematic review of the pharmacoepidemiologic studies that investigated this topic.

2. Search strategy

A bibliographic search was performed in the MEDLINE (1966 - August 2017) and EMBASE (1966 - August 2017) databases. The search strategy included studies that investigated and quantified the association between offsprings and parental drug utilisation/prescription. In particular pharmacoepidemiological and epidemiological studies, including case-control, retrospective, longitudinal, prospective, and cross-sectional studies were included. The

search was limited to studies published before the 01/09/2017, to the mesh term “humans”, and published in English language.

The base search performed contained the following mesh terms and keywords in the title and abstract:

(drug utilization[Mesh] OR drug utilization[tiab] OR drug prescriptions[Mesh] OR drug prescription*[tiab] OR self medication[Mesh] OR self medication[tiab] OR medicin*[tiab]) AND (child[Mesh] OR children[tiab] OR infant[Mesh] OR infant*[tiab] OR newborn[Mesh] OR newborn*[tiab] OR adolescent[Mesh] OR adolescent*[tiab] OR pediatrics[Mesh] OR pediatric*[tiab] OR childhood[tiab])

This strategy found 40,674 results in pubmed and 55,329 results in Embase. The search strategy was further restricted to those studies including maternal or parental informations and to epidemiological observational type of studies. The following mesh and keywords in the title and abstract were employed:

(mother*[tiab] OR mothers[Mesh] OR father*[tiab] OR maternal[tiab] OR paternal[tiab] OR parents[Mesh] OR parent[tiab] OR parents[tiab]) AND (epidemiologic studies[Mesh] OR epidemiologic[tiab] OR pharmacoepidemiology[Mesh] OR pharmacoepidemiolog*[tiab] OR pharmaco-epidemiolog*[tiab] OR case-control[tiab] OR retrospective[tiab] OR cohort[tiab] OR longitudinal[tiab] OR prospective[tiab] OR cross-sectional[tiab]).

After this step 1620 studies were retrieved in Pubmed and 2844 in Embase. Since the search strategy was very broad we excluded the following category of studies by using relevant mesh terms and key words:

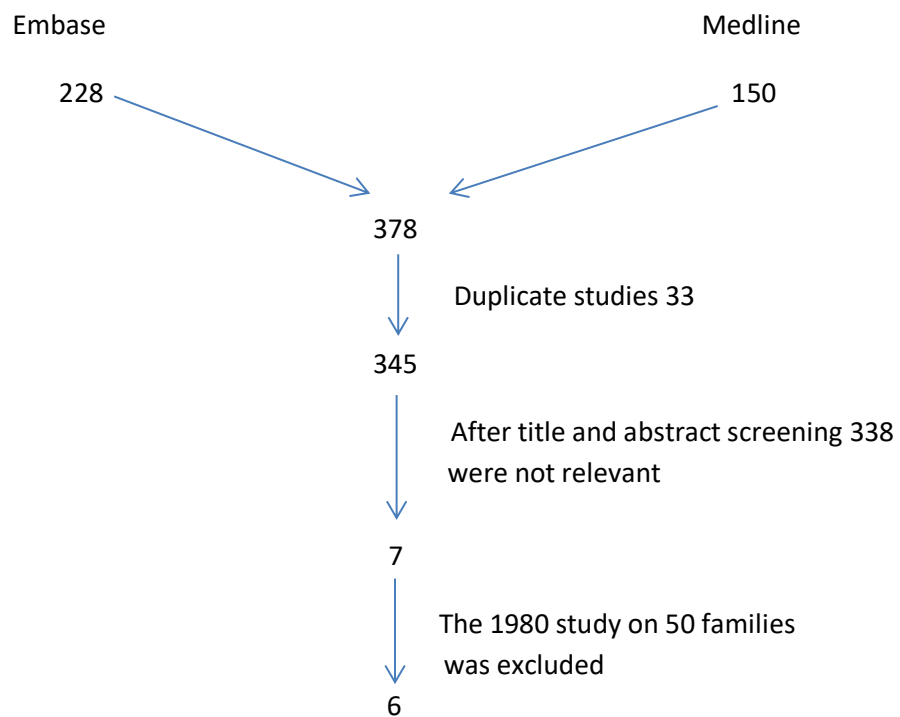
- editorials, commentaries, case reports, guidelines and lectures;
- studies about congenital abnormalities and birth defects;
- studies about illicit substance abuse, addictive behaviour and other substance-related disorders;

- studies about the vertical transmission of infectious diseases and mother-to-child transmission of other diseases;
- studies about inpatients, conducted in hospitals, in intensive care unit or concerning surgical procedures;
- studies concerning alternative or traditional medicine or complementary therapies;

In order to restrict the search to those studies that investigated an association between the variables studied, we further refined the search by using the following key words as free text in the articles' titles and abstracts: association*, associated, relation*, prediction*, correlation*, determinant*, factor*, comparison*, compare*, influence*. After the bibliographic search a total of 150 studies were found in Medline database, and 228 studies were found in the Embase database. A total of 33 studies were duplicates, thus the number of unique studies retrieved was 345. The titles and abstracts of the studies retrieved were read, and a total of 7 relevant studies were identified. The full text of the selected studies was screened, and a manual search of bibliographies was also conducted to identify additional pertinent studies. The only 1980 study on 50 families was excluded in order to have a more homogeneous sample of studies in respect to sample size and year of publication. Finally, six studies were included in the review, Figure 2. The PRISMA guideline was partially followed for this study, besides the fact that an appropriate checklist was not found for this kind of studies.

All the references have been collected and analysed using the software Reference Manager, version 11 (Institute for Scientific Information, Berkeley, California).

Figure 2 – Study selection



3. Data extraction

The following data were extracted and tabulated from each study: type of study (e.g. retrospective, prospective, survey, etc..), number of subjects included, age of children, which drug class was investigated, the statistical methods, topic of the study (relevant to the review), the quantification of the outcome of interest. The included studies were too heterogeneous to permit meta-analysis. Therefore, we qualitatively synthesized the results according to endpoints of interest.

4. Results

a. Characteristics of studies

Out of 345 studies initially identified six studies were selected. Five out of six studies were from North-Europe (two from Norway, one from Denmark, Finland, The Netherlands) and

one study was from Brazil. Three study were surveys (two cross-sectional and one part of a prospective study), and three were retrospective cohort studies using prescription and visit databases as data sources. All the included studies were published after 2010. The total sample size ranged from 131 to 97.574. The studies included children from widely different age ranges, Table 2 (ordered by the class of drugs investigated, starting from the studies investigating all drug classes).

Table 2 – Characteristics of the studies

Author	Year	Type of study	Country	Number of subjects	Age	Topic of interest	Significant association found
De Jong	2012	Retrospective cohort (database)	The Netherlands	6,731	≤5	Parental chronic prescription of drugs (at least three times per year), and recurrent antibiotic prescription vs no use of antibiotics (until five years old) in the children	Yes, but not with all the drug classes studied
Hameen -Anttila	2010	Survey	Finland	4,121	<12	Parental use of any drug (prescribed and OTC) and use of any drug in children	Yes
Log	2013	Retrospective cohort (database)	Norway	97,574	15-16	Repeated opioid and analgesic prescriptions in mothers and adolescents	Yes
Jensen	2014	Survey	Denmark	131	6-11	Maternal recurrent (monthly) use of analgesics and children use of analgesics and/or paracetamol (within 3 months)	Yes. Not for paracetamol
Bertoldi	2010	Prospective cohort (survey)	Brazil	4,452	11-12	Maternal use of hypnotics and/or sedatives (month before the survey), and use of any drug in adolescents in previous 15 days.	Yes
Holdo	2013	Retrospective cohort (database)	Norway	59,325	≤ 3	Parental use of hypnotics (1 year before pregnancy) and children chance to receive alimemazine (0-3 years old)	Yes

The studies quantified the association between children and parental use of drugs by referring to different drug classes and using different outcomes. The drug classes that were investigated in parents were: any drug (two studies), opioid or other OTC analgesics and FANS (two studies), and sedatives and/or hypnotics (two studies). The drug classes that were investigated in children were: any drug (two studies), opioids and FANS, antibiotics, OTC analgesics, , and alimemazine, Table 3.

Table 3 – Summary of the main outcomes of the studies

Author	Type of study	Outcome		Statistical method
		mother/parents	child	
De Jong	Retrospective cohort	Chronic prescription (at least three times per year)	Recurrent antibiotic prescription vs no use of antibiotics	chi squared
		mother 11.3% 6.3% father 13.1% 9.5%	- recurrent prescriptions - no prescription - recurrent prescriptions - no prescription	
Hameen-Anttila	Cross sectional (survey)	Use of any drug (prescribed and OTC)	Total use of medicine (% of treated children)	Multivariable logistic regression
		- Prescribed medicine - No prescribed medicine - OTC medicine - No OTC medicine	26.0% 35.5% p<0.005 27.8% 34.6% p<0.005	
Log	Retrospective	Repeated prescription	Repeated prescription (prevalence %)	Multivariable logistic regression
		Opioids No Yes NSAIDs No Yes	Opioids 2.4% 8.4% NSAIDs 5.1% 9.4%	
Jensen	Cross sectional (survey)	Recurrent use of analgesics (monthly)	Analgesic use OR 3.00 (1.33-6.73) Paracetamol use	Multivariable logistic regression

OR 2.54 (0.93-6.92)				
Bertoldi	Prospective cohort (survey)	Use of hypnotics and/or sedatives (month before the survey)	Use of any drug (prevalence)	Multivariable Poisson regression
		No use	29.4%	
		At least one hypnotic or sedative	38.6%	
		Both	41.1%	
Holdo	Retrospective cohort	Past use of hypnotics (1 year before pregnancy)	Chance to receive alimemazine	Multivariable logistic regression
		Mother, benzodiazepine	OR 3.0 (1.4-6.7)	
		Father, benzodiazepine	OR 3.1 (1.5-6.5)	
		Mother, hypnotics	OR 2.2 (1.7-2.9)	
		Father, hypnotics	OR 1.6 (1.1-2.2)	
		Number of hypnotic prescriptions		
		None	OR = 1	
		1	OR = 1.9 (1.4-2.5)	
		2+	OR = 2.5 (1.8-3.4)	

Concerning the statistical methods five studies used multivariable regression analyses (four studies logistic regression, and one study Poisson regression), while one study used univariable analysis methods (chi-squared, odd ratios or relative risks). Three studies reported the outcome of interest in both parents, and three studies reported only maternal drug prescription or use. An estimation of the main outcome related to the amount of drug used or prescribed was made in two studies. Two studies investigated recurrent or chronic drug use or prescription.

b. The association between child and parents drug prescription or use

Almost all of the studies retrieved registered a significant association between the children drug prescription or use, and that of their parents (mother only, or both parents), Table 2.

The study by de Jong et al. [15] investigated the association between the prescription of any drugs in parents, and antibiotic prescription in children. The authors showed that mothers whose children recurrently received antibiotic prescriptions, received at least three prescriptions each year of any drug in 11.3% of cases, while mothers whose children received no antibiotic until 5 years of age received at least three prescriptions each year in 6.3% of cases ($p < 0.001$). A similar association was observed in fathers (13.1 vs 9.5%; $p < 0.001$). This study did not use any multivariable regression technique, however it was the only study that reported the association by drug class separately for mother and father, and the association for each drug class. Of the 16 drug classes investigated, three resulted in a significant association in both parents: NSAIDs, antacids, drugs for obstructive airway diseases. In particular mothers whose children recurrently received antibiotic prescriptions had a relative risk of receiving NSAIDs 4.7 (2.6-8.6) times higher than those mothers whose children received no antibiotic. The relative risk for father was lower (1.9; 95% CI 1.0-3.5). The relative risks for antacids and drugs for obstructive airway diseases were respectively 2.2 (1.1-4.6) and 2.5 (1.6-3.8) for mothers; and 1.8 (1.2-2.7) and 1.6 (1.0-2.4) for fathers. The relative risk was increased only in mothers concerning the prescription of antihistamines 3.8 (1.8-8.0), hypnotics and sedatives 3.4 (1.1-10.5), analgesics 3.3 (1.8-6.2), anxiolytics 2.4 (1.3-4.6), and antidepressants 1.6 (1.1-2.4). The relative risk was increased only in fathers, but not in mothers, concerning cardiovascular drugs 1.6 (1.0-2.5). A significant association was not observed for drug classes such as dermatological steroids, antipsoriatics, laxatives, drugs for diabetes, antiepileptics, antipsychotics, and psychostimulants.

Concerning the use or prescription of any drug, only the study from Hameen-Anttila et al. [39] investigated this topic at the same time in parents and children by using univariable and multivariable analysis. In this study children whose parents currently used at least a prescribed medicine were significantly (χ^2 ; $p < 0.005$) more exposed to a medicine themselves (35.5%) than children whose parents did not (26.0%). Similar results were observed for OTC medicine. The authors also used a logistic regression multivariable analysis adjusting for sex, age, health status, symptoms experienced, illnesses diagnosed by physician, obtaining that children whose parents currently used at least a prescribed or an OTC medicine had a higher chance (respectively OR 1.43; 1.21-1.70, and OR 1.20; 1.01-1.44) to receive a prescribed medicine than children whose parents did not.

Two studies investigated analgesic/NSAIDs use or prescription. Jensen et al investigated maternal recurrent (monthly) use of analgesics and children use of analgesics and/or paracetamol (within 3 months) [40]. The study design was a cross-sectional survey, and they used a multivariable logistic regression to assess the strength of the associations by adjusting for a number of covariates such as child pain, mother self-rated health, mother chronic pains, mother use of analgesics, mother chronic disease and general background information (sex, age, household income, etc..). The chance of the children being treated in the last three months with analgesics was 3.0 (1.3–6.7) times higher if the mother used monthly an analgesic, while the association was found not significant if the analysis was restricted only to paracetamol use (OR 2.5; 95% CI 0.9–6.9). Log et al investigated repeated opioid and analgesic prescriptions in mothers and adolescents through a retrospective cohort database study [41]. This study had a large sample size (about 100,000 individuals) and used multivariable logistic regression adjusting for mother's socioeconomic characteristics and offspring gender. The percentage of repeated prescription opioid users was higher among adolescents whose mother was repeatedly prescribed opioids (8.4 %) than among those whose mother was not repeatedly prescribed opioids (2.4 %). A similar proportion (9.4% vs 5.1%) was observed for the prescription of NSAIDs. The results of the

multivariable analysis showed an adjusted OR of 3.1 (2.7-3.6) for opioids, and 1.8 (1.7-2.0) for NSAIDs.

Two studies investigated hypnotics use.

The study of Bertoldi et al. [42] was a survey investigating maternal use of hypnotics and/or sedatives in the month before the survey, and use of any drug in their children in the previous two weeks. The study used a multivariable Poisson regression analysis by using the chance to receive a drug as the outcome measure. The percentage of children receiving a drug was 29.4% in children whose mother did not use hypnotics nor sedatives, 38.6% in children whose mother used either one hypnotic or sedative, and 41.1% in children whose mother used both. The final results of the multivariable model indicated an higher chance to receive a drug for children whose mother used either one hypnotic or sedative (OR 1.24; 95% CI 1.06-1.45), or used both (1.40; 95% CI 1.21-1.62). The model was adjusted for variables such as: gender, household assets index, lifestyle, health status, education, complication in pregnancy.

Holdo et al. investigated the association between parental prescription of hypnotics (1 year before pregnancy) and children chance to receive alimemazine (0-3 years old) [17]. The authors quantified the risk for mother and father separately, and for benzodiazepine and non-benzodiazepine hypnotics by using a logistic multivariable regression model. The model was adjusted for mothers' use of antidepressants, mothers' smoking for both genders and mothers' parity for boys. Children whose mothers used benzodiazepine hypnotics were 3.0 (1.4-6.7) times more likely to be prescribed alimemazine than children of mothers who did not. Similar findings were found for fathers (OR 3.1; 95% CI 1.5-6.5). The same association was investigated for non-benzodiazepine hypnotics and the ORs were 2.2 (1.7-2.9) for mothers, and 1.6 (1.1-2.2) for fathers. The association increased at increasing number of hypnotics prescriptions received: OR 1.9 (1.4-2.5) for male children (for females OR 1.7; 95% CI 1.2 to 2.4) whose mother or father received one hypnotic prescription (compared to no prescriptions of hypnotic), and OR 2.5 (1.8-3.4) for male

children (for females OR 1.7; 95% CI 1.1 to 2.6) whose mother or father received two or more prescriptions.

5. Discussion

The review of the literature showed that the association between offspring and parental drug prescription or use is not widely studied, in fact, only six recent study were found. The first study concerning this topic appeared in 1980 on the BMJ and was a very simple retrospective study, not adjusting for maternal factors or child characteristics [38]. All the other studies were published in recent years. The six studies were retrospective cohort or surveys and most of them were from the northern Europe.

The meta-analysis of the data found was not possible because the included studies were too heterogeneous in respect to methodology, outcome measures, aims and characteristics of the study population. From the qualitative point of view the review showed that there was an association between drug use in children and their parents, and also that maternal use of hypnotics and sedatives was higher if their child previously used any drug. Besides the overall drug use or prescription, other studies investigated antibiotic drug use in children as an outcome, finding an association with overall drug use in parents, and another study found an increased psychotropic drug use.

The association between child antibiotic use and parental drug use by classes in the study by de Jong et al. showed interesting data, partially confirmed by other studies. There was an higher use of antibiotics and antiasthmatics in parents of children receiving antibiotics, compared to those who did not receive any antibiotic before 5 years old. This fact could be interpreted as an increased susceptibility to infection that is inherited by children, and conversely, lead to an increased use of antibiotic. Also anti-asthma prescriptions has been related to antibiotic prescriptions [43]. However the study showed that parental use of antacids, analgesics, NSAIDs, antidepressant and anxiolytics was associated with child use of

antibiotics, while, for example, laxatives, diabetes, antiepileptic drugs and antipsychotics were not. These drugs' indications share a common feature: they are all related to stress and anxiety [15]. These data suggest that the association between parental use of different drug classes and the use of antibiotics in children may be explained by the fact that these families are more prone to use medications and, often, to use them earlier. As suggested by other authors, antibiotic prescription is more common in families with a lower socio-economic profile, greater concerns about infectious diseases, and increased stress of fathers [30,31,44-47]. However the scenario is quite complex and this may be true for antibiotics, but not for other drugs. For example other authors suggested that OTC drugs are administered more to their children by mothers with more education and higher household incomes, even if this was not confirmed by the study of Hämeen-Anttila that showed no effect of these variables [39,48,49].

The higher maternal psychotropic drug use related to the overall child drug use was first seen in the study by Howie and colleagues in 1980. This study and the one by de Jong et al. share the fact that they did not adjust for socioeconomic and other potentially relevant parental variables because such data were not available. The studies from Hämeen-Anttila and Bertoldi and colleagues adjusted for parental background information and, while they were different in terms of design and aims, both studies showed that the chance to receive any drug or hypnotics was increased in mothers of children receiving more drug prescriptions. Compared to studies that did not adjust for family background information these two studies obtained much less strong results, yet still significant, in terms of odds ratios.

The paternal information was reported only in two out of seven studies. Usually the association with paternal drug exposure was less convincing than the association observed in mothers. This may be because mothers are usually more involved with the care of the children, and may have more opportunity to discuss prescription for their children.

Besides the different aims and methodologies of the included studies, an important limitation was the hugely variable sample size among them. The lack of statistical power was an important limitation of some of the studies, and it hindered the possibility to show differences and associations in the chance of drug exposure in subgroups. It is the case of the study by de Jong et al. In fact the number of individuals receiving different drug classes ranged from 1 to 76, leading to very large confidence intervals. This fact prevented to reach the significance for some of the drug classes analysed. Also other studies had few overall individuals included, like the study by Jensen and colleagues. In particular this study was underpowered to show a significant difference in the child chance of being treated with paracetamol when the mother used monthly an analgesic, even if the effect size was quite large (OR=2.5). Another limitation of these studies is the lack of data concerning the physician that is prescribing drugs, which is absent in all the studies retrieved. Some physicians prescribe medication more easily than others, and their influence is important in determining drug prescription in mothers and their children, especially if the physician is the same, which may be often the case in many countries.

6. Conclusions

The different outcome measures, methodology, and information available used in the studies retrieved lead to very difficult comparison among the results, and, in turn, to difficult conclusions. There is indeed evidence of an association between maternal drug use or prescription in general and children drug use or prescription. The strength of association is higher for mothers drug use more than it is for fathers, and it is higher for prescription drugs other than OTC drugs, even if only a minority of studies looked at these outcomes. Overall the studies looked at different endpoints and, thus, the association found for many drug classes has been investigated only by one or a few studies. From some of the studies the hypothesis of an increased susceptibility to infection that could be inherited by children, and conversely, lead to an increased use of antibiotic seems possible. However

there are also indication that mainly the kind of drugs that are related to stress and anxiety are related to drug use in the offspring, and this could means that some families are more prone to use medications and, often, to use them earlier.

A study on this topic was not possible to conduct in this PhD thesis because a deterministic link between mother and child was not possible with these databases. There is a need for more studies looking at the association between child and parental drug use or prescription since there is not a standardised methodology to conduct such studies, there are a number of possible endpoints of interests, and the sample size is often non-sufficiently large. Finally there is a need for more studies that includes information about cultural, behavioural and socio-economic backgrounds, since the literature shows that these variables may be among the most important factors influencing drug use in the family.

V. Determinants of drug prescribing: drug utilisation studies in paediatrics

A. Antibiotic and anti-asthmatic drug prescriptions in Italy: geographic patterns and socio-economic determinants at the district level

1. Introduction

The prevalence of drug prescription in Italian children is among the highest in Europe and the most frequently prescribed classes are antibiotics and anti-asthmatics [50].

As already described, large qualitative and quantitative differences in antibiotic exposure between countries have been found [4]. Wide differences have also been observed in children's exposure to anti-asthmatics between different countries: prevalence (percentage of children receiving at least one prescription in a year) ranges from 6.2% in Norway to 19% in Italy [5]. β 2-mimetics and inhaled steroids are the most frequently prescribed anti-asthmatics in Italy and their use is, respectively, threefold and fourfold higher than in UK and in the Netherlands [9]. In Italy the prevalence of anti-asthmatic drugs is much higher than prevalence of disease, indicating that anti-asthmatics are over-prescribed [9,23].

In Italy the prevalence rate for all drugs prescribed to children and adolescents is 57.3% in the North, while it is 68.3% in the South [50]. The prescription profile of antibiotics has been extensively described at the regional level. The highest prevalence rate is found in southern regions and differences at the LHU level range from 35.6% to 68.5% [6]. Under use of recommended drugs, such as amoxicillin, is an issue, especially in the southern part of the country, with an excessive exposure to second choice treatment (i.e. oral and parenteral cephalosporins) [6]. Notable differences have been demonstrated also within regions, as is the case in the Lombardy Region, where the prevalence rate for all drugs ranged from 38.4% in Milano's LHU to 54.8% in Brescia's LHU in 2006 [20]. The anti-asthmatic prescription patterns within Italy have not been investigated in depth, however, it is known that beclometasone (which is often related to inappropriate or unlicensed use in Italian children) is the most used anti-asthmatic drug and is most used in the South [8,51].

In this context a comparison between the two most used drug classes (that are characterised by high inappropriateness of use in Italy) at a district level was made. Three prominent regions were included: Lombardy, Lazio, and Puglia. The aim of this study was to evaluate the antibiotic and anti-asthmatic drug prevalence rate at the district level as well as the influence of territorial setting, including a few socio-economic determinants, on an Italian child and adolescent outpatient population.

2. Methods

a. Data source

Data sources were regional databases routinely updated for administrative and reimbursement reasons. The databases stored all community prescriptions reimbursed by the NHS. The study population was composed of 3,301,096 children and adolescents <18 years old (32.5% of the population <18 years old), living in three large Italian regions: Lombardy (1,616,268 resident children), Lazio (926,015) and Puglia (758,813), from North to South. The observation period was from 1 January to 31 December 2008 for all regions. Overall, 193 healthcare districts (45 in Puglia, 55 in Lazio and 95 in Lombardy Region), participated in the study. The cities of Rome and Milan were considered as a whole and not as “composed by districts”, because data on such aggregation level were not available. Two of 95 districts from Lombardy Region were excluded from the analyses because their paediatric population size was under the first percentile of the distribution of the population by district. The average number of resident children/adolescents in each district was 16,932 (ranging from 16,237 in Lazio to 17,375 in Lombardy Region).

All drugs were classified according to the ATC system (Anatomical Therapeutic Chemical classification system). In this study antibiotics were considered as every drug belonging to the J01 sub-group and anti-asthmatic as to every drug belonging to the R03 sub-group.

b. Measures

In order to describe the prescription profile the prevalence rate for antibiotics and anti-asthmatics was calculated at the district level. The prevalence rate was the number of individuals who received at least one prescription in one year, divided by the number of children/adolescents.

The all-cause hospitalisation rate and hospitalisation rate for asthma as primary or secondary diagnosis were calculated by district, expressed as the number of patients admitted to the hospital at least once in one year (ordinary admissions) divided by 1000 resident children/adolescents. Data were retrieved from hospital discharge records, which include information on primary diagnoses and up to five co-existing conditions such as secondary diagnoses, procedures performed, date of admission, discharge, and in-hospital death. Asthma diagnoses were classified according to ICD9 (International Statistical Classification of Diseases and Related Health Problems) code 493. The number of FPs per 1000 resident children under 12 years old was calculated by district.

Demographic distribution among the three age strata (0-5, 6-11 and 12-17 years old) was heterogeneous across the districts, possibly influencing prevalence. In order to adjust prevalence by age a standardisation method was applied. A logistic regression analysis, using the Lombardy Region database to evaluate the association between drug prescription and age, was performed [20]. The adjusted odds ratios (see the previous reference for details) were used as “weight” in the standardisation and were calculated for three age-strata: ≤ 5 years old (OR=1.77), 6 to 11 years old (OR=1), and 12 to 17 years old (OR=0.70). By using the age-specific weight and prevalence, the age-corrected prevalence for each district for antibiotic and anti-asthmatic drugs were obtained [52,53]. All data analyses were performed using the age-corrected prevalence.

An indirect standardisation method was also applied to prevalence for antibiotics and anti-asthmatics in all districts in order to calculate the standardised prevalence ratio (SPR). The indirect standardisation uses age-specific prevalence from the overall population to derive the numbers of expected cases in the region’s population (i.e. district). SPR indicates whether the prevalence rate observed at a district level is significantly higher or lower than what would have been observed in the standard population. Confidence intervals were calculated with a shortcut method [54]. Districts with a SPR that is significantly lower than 1

will be referred to as “lower than expected” and those having a SPR significantly higher than one as “higher than expected”.

$$SPR = T_{obs} / T_{exp} = T_{obs} / [\sum_{age\ groups} (P_{as} N_{as})]$$

SPR = Standardised prevalence ratio

T_{obs} = number of treated children (district).

T_{exp} = number of expected treated children (district)

P_{as} = age-specific prevalence rate (standard population).

N_{as} = number of people in the age-specific group (district).

A choropleth map of SPR for antibiotics and anti-asthmatics was elaborated at the district level [12]. The map was created using the software Arcmap 10.1.

The non-parametric Spearman test was used to evaluate the correlation between antibiotic and anti-asthmatic prevalence and some determinants including: average annual income per inhabitant, latitude, number of FPs per 1000 resident children, and hospitalisation rate for all causes and for asthma.

The ANOVA test and the Bonferroni post-hoc test were used to compare the prevalence rate by districts in the three regions. The chance of receiving an antibiotic or anti-asthmatic prescription for children resident in districts with a lower average annual income per inhabitants (lowest quintile) versus a higher average annual income (highest quintile) was calculated. The coefficient of variation (CV) was used to assess the variability of district prevalence among LHUs.

3. Results

a. Regional prescription profile

During 2008, 1,861,425 children and adolescents (56.4% of the study population) received at least one drug prescription. Antibiotic prevalence rate was, on average, 47.9%, ranging from 44.1% in the Lombardy Region to 57.5% in the Puglia Region.

Table 4 – Average district prevalence (%) and anova test on the prevalence rates grouped by region

	antibiotic drug prevalence (%)		anti-asthmatic drug prevalence (%)	
	range	mean \pm sd	range	mean \pm sd
Lombardy (95)	34.0-55.1	44.1 \pm 4.1	11.7-26.0	17.8 \pm 3.3
Lazio (55)	35.6-66.7	49.8 \pm 6.7	17.3-32.4	25.1 \pm 3.6
Puglia (45)	48.0-67.9	57.5 \pm 4.9	17.4-35.5	26.5 \pm 4.6
ANOVA test	F= 105.26	p< 0.0001	F=112.30	p< 0.0001

Anti-asthmatic prevalence was, on average, 21.4%, ranging from 16.9% in Lombardy to 27.0% in Puglia. The male/female odds ratio for prevalence for antibiotics was, on average, 1.05 (95% CI 1.05-1.06), with no significant differences between regions, while for anti-asthmatics it was 1.21 (1.20-1.21) with a slightly higher ratio in Lombardy (1.24; CI 1.23-1.25) compared to Lazio and Puglia (1.18; CI 1.17-1.19).

b. Prescription profile at the district level

The age-corrected prevalence for all drugs ranged from 41.0% to 74.7%, from 34.0% to 67.9% for antibiotics and from 11.7% to 35.6% for anti-asthmatics. The age-corrected and crude prevalence differed significantly only in a few districts that had a small population size. The ANOVA and Bonferroni tests showed a significant difference in the prevalence of antibiotic and anti-asthmatic drugs in districts across the three regions (Table 4; p<0.001),

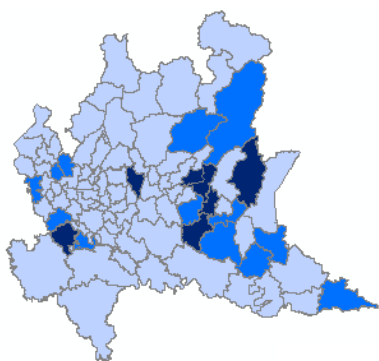
with the exception of anti-asthmatic prevalence in Lazio and Puglia ($p=0.19$). Prevalence was much lower in Lombardy Region compared to the other two regions, considering both antibiotics and antiasthmatics.

SPR ranged from 0.70 to 1.44 for antibiotic drugs and from 0.54 to 1.72 for anti-asthmatic drugs, Figure 3. In Lombardy 69% of the districts (66/93) had a SPR lower than expected for both anti-asthmatics and antibiotics. On the contrary, in Puglia, no district had a SPR lower than expected and in 82% of them (37/45) the SPR was higher than expected. Only a few districts in Puglia had an antibiotic and antiasthmatic prevalence comparable to those in Lombardy Region. Large differences were observed in the variability of district prevalence within each LHU: CV ranged from 0.01 to 0.15 for antibiotics and from 0.03 to 0.22 for anti-asthmatics.

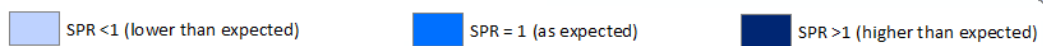
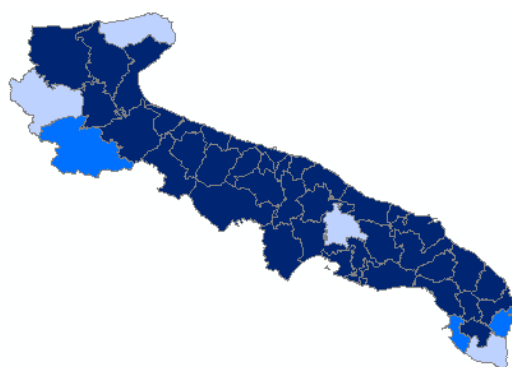
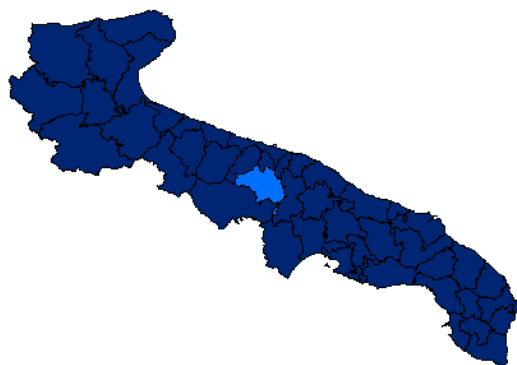
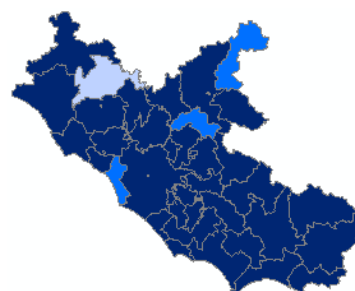
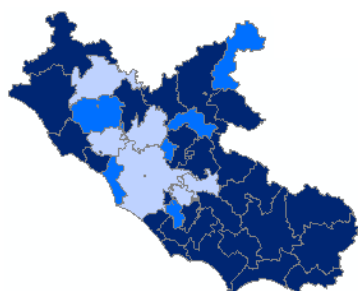
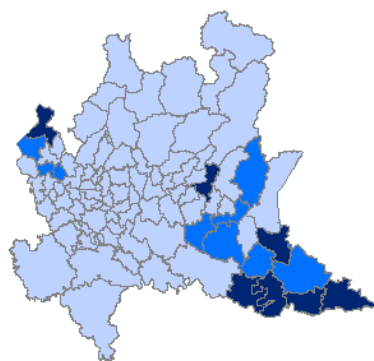
The median average annual income per inhabitant was 7,187 € (interquartile range, IQR = 6,440-8,262 €) in the high-prevalence districts (districts having both antibiotic and anti-asthmatic drug prevalence over the mean plus one SD), while it was 15,360 € (IQR = 13,358-16,837 €) in the low-prevalence districts (prevalence under the mean minus one SD).

Figure 3 - Choropleth map of the standardised prevalence ratio (SPR) at the district level for antibiotics and anti-asthmatics. The SPR indicates whether the prevalence observed in each district is significantly higher ($SPR>1$) or lower ($SPR<1$) than expected by using a standard population as a reference (the overall study population).

Antibiotics



Antiasthmatics



c. Determinants

The Spearman test scored a significant positive correlation between antibiotic and anti-asthmatic prevalence at the district level ($r_s = 0.77$; $p < 0.001$). The within-region correlation was significant, but less strong, especially in Lombardy ($r_s = 0.57$; $p < 0.001$) and Puglia ($r_s = 0.50$; $p < 0.001$).

There was a significant inverse correlation between average annual income per resident and both the prevalence of antibiotics ($r_s = -0.77$ $p < 0.001$) and anti-asthmatics ($r_s = -0.73$ $p < 0.001$). Children resident in districts in the lowest quintile of annual income per resident had a higher chance (highest vs lowest quintile) of receiving an antibiotic (OR 1.75, 95% CI 1.74-1.77) or anti-asthmatic drug (OR 1.56, 95% CI 1.55-1.57), Table 5.

The correlations between prevalence of antibiotic and anti-asthmatic drugs toward other determinants are reported in Table 6. Latitude was inversely correlated with antibiotic and antiasthmatic prevalence. There was not a correlation between hospitalisation for asthma and antiasthmatics prevalence. The number of FPs per 1000 inhabitants was not relevantly correlated with prevalence.

Table 5 – Analysis of the correlation between antibiotic (J01) and anti-asthmatic (R03) prevalence versus average annual income per resident at the district level, numbers in brackets are confidence intervals.

prevalence	average annual income at the area level
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	overall	lowest vs highest quintile
	rS	OR
Lombardy		
antibiotics	-0.27	1.23 (1.22-1.24)
anti-asthmatics	-0.46	1.25 (1.24-1.27)
Lazio		
antibiotics	-0.55	1.31 (1.30-1.33)
anti-asthmatics	-0.38	1.16 (1.15-1.18)
Puglia		
antibiotics	-0.34	1.29 (1.27-1.30)
anti-asthmatics	-0.02*	1.03 (1.02-1.05)
Total		
antibiotics	-0.77	1.75 (1.74-1.77)
anti-asthmatics	-0.73	1.56 (1.55-1.57)

*non-significant p-value (>0.05)

Table 6 – Correlation between prevalence of antibiotic and anti-asthmatic drugs vs other determinants at the district level

prevalence vs:	rS	p-value
Latitude (South to North)		
antibiotics	-0.71	<0.001
anti-asthmatics	-0.72	<0.001
Hospital admission rate		
antibiotics*	0.33	<0.001
anti-asthmatics°	0.03	0.65
FPs per 1000 inhabitants		
antibiotics	-0.19	0.01
anti-asthmatics	-0.02	0.80

*all cause hospitalisation rate

° hospitalisation rate for asthma

4. Discussion

This is the first Italian study evaluating antibiotic and anti-asthmatic prescriptions at the district level in three large Italian regions. The result concerning antibiotics was similar to what was observed, at the LHU level, in a previous study [6], although prevalence rate ranges at the district level were wider than those found in the previous study (e.g. in Lombardy the range was 34.0-55.1% at the district level, while it was 36.3-50.6% at the LHU level). In particular, this study underlines the fact that, even in settings characterised by low prevalence (i.e. Lombardy), there are districts with a higher prevalence than expected and that variability is often very high even among districts within the same LHU. The use of anti-asthmatics was found to be higher than in a previous study in children (same age group) in the North [23], while it was similar to what was observed in another Italian paediatric population [55].

The current study shows that the use of anti-asthmatics, as well as antibiotics, is higher in the South and that there is a correlation between anti-asthmatic and antibiotic use at the district level. In particular, the SPR (for both antibiotics and anti-asthmatics) increases from North to South. Another study already showed that Italian children living in the South have a greater chance of receiving a prescription of any drug compared to their counterparts living in the rest of the country [8]. Since antibiotics and anti-asthmatics are the most commonly prescribed drugs in Italy this finding is in part expected and may mean that the geographical differences observed may not be linked to a particular class of drugs, but to other, independent factors.

The association between asthma and antibiotic use in children has already been shown in the literature [56-58]. The relationship between anti-asthmatic and antibiotics prescription, however, is a quite different phenomenon. In fact, particularly in Italy, anti-asthmatic drug consumption in an outpatient setting is not a good disease indicator, since the inappropriate use of this drug class is very high [9]. The unreliability of anti-asthmatic consumption as a disease indicator in this setting is evident if one looks at its association

with hospitalisations for asthma: they are unrelated. For this reason the correlation among the use of these two drug classes probably is thought to be due to a generalised inappropriate use of drugs and not to the asthma-antibiotic use link.

Concerning income, children living in low income districts have a higher chance of receiving a prescription of an antibiotic or an anti-asthmatic. This trend persists within regions/areas characterised by different prescribing volumes. The finding that there is a twofold absolute difference in the average annual income per inhabitant between the high and the low prevalence districts is striking. Similar findings have been recently found in Germany [59] and in Switzerland as well [60]. In these countries, as in Italy, the cost of antibiotic and anti-asthmatic drugs is, at least partially, reimbursed. In these cases, given the methodology used, the confounding role of out of pocket drug use cannot be excluded [8].

Concerning latitude, the prevalence is higher in southern Italy, but this is not true in Germany, where antibiotic use is higher near the upper-western border and the far north. The inverse correlation between latitude and antibiotic/anti-asthmatic drug prescription is valid in Italy, where the North-South socio-economic polarisation is well known, but not necessarily in other countries. Another study on antibiotic prescriptions found that in Lombardy there is a West-East geographic trend more than a North-South one [12]. In this study, latitude and average annual income were both related to prevalence of antibiotics and anti-asthmatics (the two indicators are co-linear) but the hypothesis is that income is a more relevant variable, because, when looking at prescriptions within regions of different income levels, a similar, even if weaker, association persists.

A plethora of other factors possibly associated with drug prescription to children (mainly antibiotics) have been considered in a number of international and Italian studies [13,14,61-65]. Education and income level are factors known to indirectly affect individual health. Various studies agree in demonstrating that poor and less educated people have

inadequate access both to primary prevention and to early diagnosis [66]. These facts could also reflect a lower quality of children's healthcare. A lower educational level could also affect the understanding of the therapy's importance and, indirectly, how much the prescriber perceives the parental expectation of a prescription, the latter of which is a known factor influencing the physician's decision [13]. It has been demonstrated that parents of children receiving many antibiotics use more medicines themselves [15]. These data reinforce the hypothesis that area income deprivation is only a proxy of other linked deprivations, which are probably more relevant or more directly affect the amount of prescriptions in children. In particular educational deprivation, which is very often related to income deprivation [67], may have, at least in part, a causal role in the amount of medicines prescribed to children. The role of the prescriber is also particularly important: in Lombardy, in the highest prevalence areas, a higher number of FPs classified as high prescribers was found [12].

Ultimately, the current study shows that prescribing distribution at a micro-level is associated with socio-economic inequalities, even if the Italian NHS fully reimburses antibiotics and anti-asthmatics. A recent study in the same setting (Lombardy Region) showed that a local educational intervention on FPs was able to improve the prescription profile [22]. If education (of families and physicians) is one of the most important factors affecting prescribing, policy makers should take into account the differences highlighted in order to plan educational interventions to reduce prescription and implement a more rational drug use.

Finally, as a methodological issue, this study underlines the importance of the evaluation of epidemiological outcomes also in small census areas. The prescription profile of a region cannot be representative of the national pattern. On the other hand, the profiles observed at the national and regional levels are not applicable at the district level. From this point of

view, the local context influences drug prescriptions and its role should be investigated as part of the monitoring of drug utilisation.

a. Strengths and weaknesses

This study is able to provide more robust data on the association between income and prescription of reimbursed drugs to children by including an analysis of data at the district level. The entire child/adolescent population of three regions, representative of different geographical and economic settings, was included, avoiding selection bias (e.g. different social or educational backgrounds). The prevalence by age, which is the most important factor associated with a higher drug prescription in children, was standardised in this study. However, some limitations must be considered.

Since reimbursement data were analysed, it was not possible to ascertain adherence to prescribed treatments. This is a limitation because other studies on adult patients reported low adherence rates in primary care [68], even if in paediatric patients the phenomenon may be limited. The use of aggregated data precluded the application of more appropriate statistical methods such as logistic regression analysis. Furthermore, data on out of pocket drug use was not available for antibiotics and anti-asthmatics (although they are fully reimbursed). Out of pocket drug use could potentially bias the relationship between higher anti-asthmatic and antibiotic drug consumption and lower income as described elsewhere [8]. However, it is likely that the phenomenon is limited for reimbursed drugs.

5. Conclusions

The current study highlights anti-asthmatic and antibiotic prescription differences at the district level showing wide local differences and specificities that were not demonstrable in other studies. Anti-asthmatic and antibiotic drug prescribing are related and their use is higher in the South of Italy. The data confirm the presence of an inverse association between annual income and the prevalence of antibiotic and anti-asthmatic drugs also at

the district level. Local socio-economic inequities can concur in prescribing distribution and must be considered when planning educational interventions to reduce prescription and increase rational drug use.

B. A multiregional study about psychotropic medicine prescriptions

1. Introduction

Paediatric psychopharmacology has developed rapidly over the last few decades. Large randomised clinical trials focused on the treatment of a spectrum of psychiatric illnesses - such as ADHD [69], bipolar mania[70], behavioural problems associated with autism [71], and depressive [72] and anxiety disorders [73] – have been published, and the emphasis on pharmacological treatments has grown considerably.

As an increasing number of young patients began to receive psychotropic drugs, attention to the safety profile of such drugs in paediatric patients increased. In 2004 the US Food and Drug Administration (FDA) issued a safety warning – the so called “black box” warning - about the twofold higher risk of suicidal behaviour in adolescents receiving antidepressants [74]. Other important safety issues emerged, such as the increasing awareness of adverse metabolic effects of second-generation antipsychotic medicines [75], and the abusive potential of psychostimulants [76,77]. Since then, paediatric psychopharmacology has become an increasingly relevant component of youths’ healthcare, and several drug utilization studies have been performed with the aim to evaluate psychotropic drug use and prescribing.

Large variations were found in the psychotropic prevalence among youths worldwide [26, 78-85]. Prevalence in Italy is lower (about 3‰)[78] than in Europe and in the US (up to over 6‰)[26,79]. The same general trend is noticeable in the different classes of psychotropic medications. For example, the prevalence of antidepressants ranges from over 2% in US [79] and 1.7% in Denmark [80] to 2.4‰ in Italy [78]. Concerning drugs used for ADHD the prevalence ranges from 2 to 4% in the US and Iceland, and from 1 to 2% in Australia, Canada, Israel, and the Netherlands [81-85]. A similar trend was observed for antipsychotics: they are rarely prescribed in Italy (0.7 ‰) [78], while their prevalence is about 1% in the US [79].

Large differences between countries are also present in terms of policy and resources for care and services for paediatric mental health. Only 1 in every 4 cases has access to services

in high income countries [86], while in low and middle income countries the rate can be 20 times lower [87]. These factors, together with many others, contribute to the wide gap observed in treatments worldwide, where in some countries (especially in Europe) children are more likely to be pharmacologically undertreated with respect to their clinical needs, while in the US, where such drugs are overprescribed, the opposite is true [88,89]. There is also evidence that the chance of receiving an antidepressant may vary within the same country [90], where policy and organization of services are expected to be more homogenous. In this context it is essential to monitor psychotropic drug use in youths.

Data on paediatric psychotropic medication prescription and use in Italy are sparse and not updated [27,78,91]. In fact, the only two studies published in the last five years reported data of a single region or LHU [27,91], and the only study representative of the Italian paediatric population reported 2004 data [78]. Data concerning the psychotropic drug prescription in the general population showed that there are differences in the amount of prescriptions filled at the regional level, and this could reflect differences in the prevalence of psychiatric disorders, and also in the access to psychiatric services [92]. Since a continuous monitoring and surveillance on paediatric psychotropic drug prescription is essential, we analysed the prescription of psychotropic drugs from 2006 to 2011. In order to assess for the first time differences among regions, we included seven Italian regions belonging to different geographical areas, providing a large - half of the paediatric population - and representative sample of the Italian child and adolescent population. Since there could be differences in the epidemiology of psychiatric disorders, we also collected the hospital admission rates at the regional level as a proxy of severe psychiatric illness in order to compare them to the prevalence of psychotropic drugs.

2. Methods

a. Data source

Data sources were regional databases routinely updated for administrative and reimbursement reasons. The databases store all outpatient (i.e. outside the hospital) prescriptions reimbursed by the NHS.

In November 2013, Italian researchers who were part of the ENCePP® (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) network [93] were asked to participate in the study.

Seven of the eleven regions contacted participated in the study: Veneto, Lombardy, Friuli Venezia Giulia, Emilia Romagna, Abruzzo, Lazio and Puglia (69 LHUs). The centres involved have a long-standing experience in pharmacoepidemiological studies, and in the analysis of health administrative databases. Each researcher provided the prescription data concerning psychotropic drug prescriptions for the paediatric outpatient population (<18 years old) in his own region, through an agreement with the Regional Ministry of Health. For the Veneto Region data were provided for 15/22 LHUs (597,596 children and adolescents, 77% of the regional population), which were those included in the CINECA consortium, a National Interuniversity Consortium constituted with the purpose of providing a friendly and efficient database that collects and monitors the GPs' prescriptions [78]. All regions provided data from 2006 to 2011. For the Abruzzo Region, data for years 2010-2011 were provided.

The study population in 2011 was composed of 5,019,564 youths less than 18 years of age living in the regions participating, representing 50.2% of the Italian population of this age. The regions were representative of different geographic areas: North of Italy (Friuli Venezia Giulia, Lombardy, Emilia Romagna and Veneto, 71.2% of the North population), Centre (Lazio, 49.9%), and South (Puglia and Abruzzo, 36.5%). The seven regions had different economic backgrounds. In particular the mean annual income per resident in 2011 in Italy was 12,159 €, and ranged from 8,382€ (Puglia) to 15,502€ (Lombardy), source: Italian ministry of Economy and Financial Affairs.

Aggregated, anonymous data were provided so ethical approval was not required.

Psychotropic drugs were defined according to the World Health Organization categories and comprised the following subgroups of the Anatomic Therapeutic Chemical (ATC) classification system: antipsychotics (N05A), antidepressants (N06A) and centrally acting sympathomimetics (ADHD medications, N06BA). Anticonvulsants (N03 subgroup) were excluded because in children they are mainly used to treat epilepsy, while anxiolytics, sedatives, and hypnotics were excluded because they are not reimbursed by the Italian NHS, and thus not retrieved in the database, as stated above.

Data concerning hospital admissions for psychiatric diagnoses were also collected at the regional level as a proxy of severe psychiatric illness in order to compare them to the prevalence of psychotropic drugs. To this purpose, the following ICD-9 codes were considered: 290 to 319.

b. Data analysis

For 2011 the following outcome measures were calculated by age and gender for the overall sample and for each region:

- Prevalence of current users, defined as the number of individuals who received at least one psychotropic drug prescription per 1,000 youths;
- Incidence of new users, defined as the number of people who received a psychotropic drug prescription for the first time (did not receive it during the previous year) per 1,000 youths;
- prescription rate, defined as the number of prescriptions per youth treated with at least one psychotropic drug in one year;
- hospital admission rate, defined as the number of resident youths admitted to hospital due to any psychiatric illness at least once in one year per 1,000 youths.

For the 10 most prescribed psychotropic drugs in 2011 the prevalence was calculated for the following age strata: 0-5, 6-11, and 12-17 years old. Furthermore, the percentage of

treated youths (number of children and adolescents who received at least one prescription of a certain drug, divided by the number of children that received any psychotropic drug prescription during one year) was calculated for each active substance.

For 2011 the main indicators (not stratified by age and gender) at the LHU level were retrieved. A choropleth map of prevalence at the LHU level was created using the software Arcmap version 10.1. The prevalence values were categorised into three classes calculated on the basis of the mean \pm 1 sd.

The temporal utilization trend of psychotropic drugs in youths in the period 2006–2011 was analysed. Prevalence, incidence, prescription, and hospital admission rates were calculated for all psychotropic drugs and for antipsychotics, antidepressants, and ADHD medications separately. The 5-year cumulative incidence of psychotropic medications was calculated for the 2007–2011 period.

The coefficient of variation (CV) was used to assess the variability in prevalence reported by LHUs among regions. The Welch's ANOVA and the Tukey post-hoc tests were used to compare the prevalence reported by LHUs in the included regions. The chi-squared for linear trend (χ^2 trend) test was used to investigate the presence of a trend in the prevalence of psychotropic, antidepressant, antipsychotic and ADHD medications over the years in the whole population studied and in each region. The area under the prevalence–time curve (AUC) was calculated according to the linear trapezoidal rule for the intervals: 0–5, 6–11, 12–17 years in respect to gender. The Pearson test was used to investigate the correlation between prevalence and prescription, hospital admission rates, latitude, longitude and average annual income at the LHU level. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using SAS software, version 9.2 (SAS, Cary, NC, USA).

3. Results

a. Overall study population



During 2011, 8,834 youths received at least one psychotropic drug prescription. The prevalence was 1.76‰ (95% CI 1.72-1.80), Table 7.

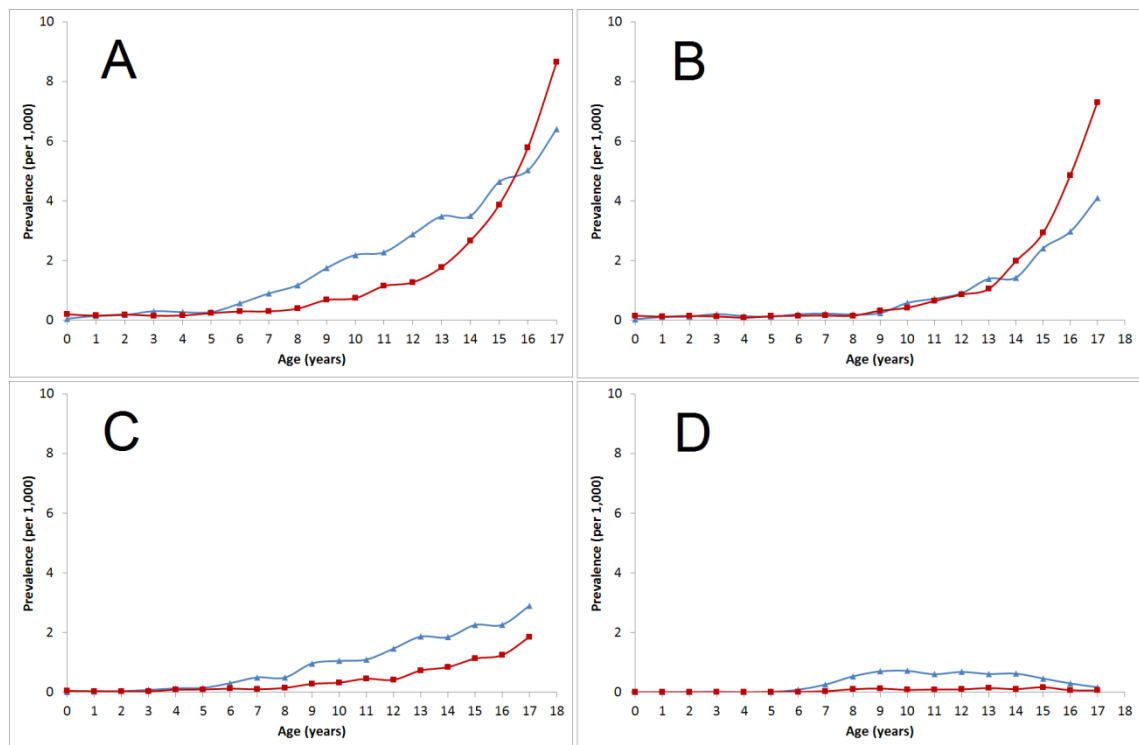
Table 7 - Number of youths 0–17 years old, number of LHUs, average prevalence of prescription, prescription and hospital admission rate percentage by region, ordered by decreasing latitude from top to bottom (year 2011)

Regions	Population (n)	LHUs (n)	Prevalence				Hospital admission rate	
			(‰)	95% CI	Range by LHU	Male/ female ratio	(‰)	95% CI
FVG*	184,553	6	2.17	1.96-2.39	1.87-2.51	1.35	3.82	3.54-4.11
Veneto	597,596	15	1.57	1.47-1.67	1.07-2.25	1.36	3.40	3.25-3.55
Lombardy	1,688,543	15	1.56	1.50-1.62	1.09-2.78	1.26	1.12	1.07-1.17
E.Romagna	695,043	11	1.97	1.87-2.08	0.97-2.30	0.97	0.66	0.60-0.73
Abruzzo	205,774	4	1.88	1.69-2.06	1.39-2.68	1.50	0.89	0.77-1.02
Lazio	925,339	12	1.96	1.87-2.05	1.43-2.22	1.28	0.60	0.55-0.65
Puglia	722,716	6	1.78	1.68-1.87	1.54-2.11	1.53	1.75	1.65-1.85
Total	5,019,564	69	1.76	1.72-1.80	0.97-2.78	1.27	1.41	1.38-1.45

*Friuli Venezia Giulia

Antidepressants were prescribed to 5,100 youths (1.02‰; 95% CI 0.99-1.04), antipsychotics to 3,512 youths (0.70‰; 95% CI 0.68-0.72), and ADHD medications to 976 youths (0.19‰; 95% CI 0.18-0.21). The mean number of prescriptions per treated youth was 4.4 for psychotropic drugs, and ranged from 3.2 for antidepressants to 6.0 for ADHD medications. The psychotropic drug prevalence increased by increasing age following an exponential trend, both in males and females, with negligible exposure in the first year of life and 7.5‰ exposed at 17 years old, Figure 4.

Figure 4 – Prevalence (per 1,000) by age and gender (Male:  Female: ) of overall psychotropic drugs (A), antidepressants (B), antipsychotics (C), and ADHD medications (D).



While antidepressants were the most prescribed psychotropic drug class in the overall population and in females ($AUC_{N06A/all\ psychotropic\ drugs} = 0.76$), antipsychotics were the most prescribed psychotropic drugs in males ($AUC_{N05A/all\ psychotropic\ drugs} = 0.48$). The prevalence of psychotropic medications was similar for males and females up to 5 years old, was higher in males in the 5-15 year range, and was higher in females afterward. Males were more exposed to psychotropic drugs than females ($AUC_{0-17\ male/female} = 1.23$), particularly in the school age ($AUC_{6-11\ male/female} = 2.52$). The disproportion was particularly evident for ADHD medications ($AUC_{0-17\ male/female} = 5.06$) and antipsychotics ($AUC_{0-17\ male/female} = 2.16$). Females were more exposed to antidepressants than males ($AUC_{0-17\ male/female} = 0.74$). With antidepressants, the trend by gender and age was very similar that of psychotropic drugs, and began to increase in pre-adolescents, with females receiving more antidepressants than boys after 15 years of age (fig.4). The prevalence of antipsychotics

began to increase in school-aged children, with males being more exposed than females at any age. For ADHD medications the highest prevalence was in nine year old children, particularly males, while the female prevalence was negligible at any age (fig.4).

The incidence of psychotropic drug prescriptions was 1.03‰ (95% CI 1.00-1.06), with no significant differences between males and females (AUC_{0-17} male/female = 1.02; 95% CI 1.00-1.05). The incidence of antidepressants was 0.69‰ (95% CI 0.67-0.72), while that of antipsychotics was 0.32‰ (95% CI 0.31-0.34), and that of ADHD medications 0.08‰ (95% CI 0.07-0.09). The 5-year cumulative incidence of psychotropic medications in the 2007-2011 period was 4.29‰, with a total of 26,142 incident cases.

The hospital admission rate was 1.41‰ (95% CI 1.38-1.45). In 2011, a total of 20 different drugs were among the list of the ten most prescribed psychotropic drugs in the participating regions, Table 8. The most prescribed psychotropic drug was risperidone (20.6% of children treated with psychotropic drugs), followed by sertraline (18,0%), and methylphenidate (7.1%).

Table 8 - The prevalence per 10.000 resident youths of the ten most prescribed psychotropic drugs in 2011 by age group. Drugs not approved for use in each age group are reported in italic.

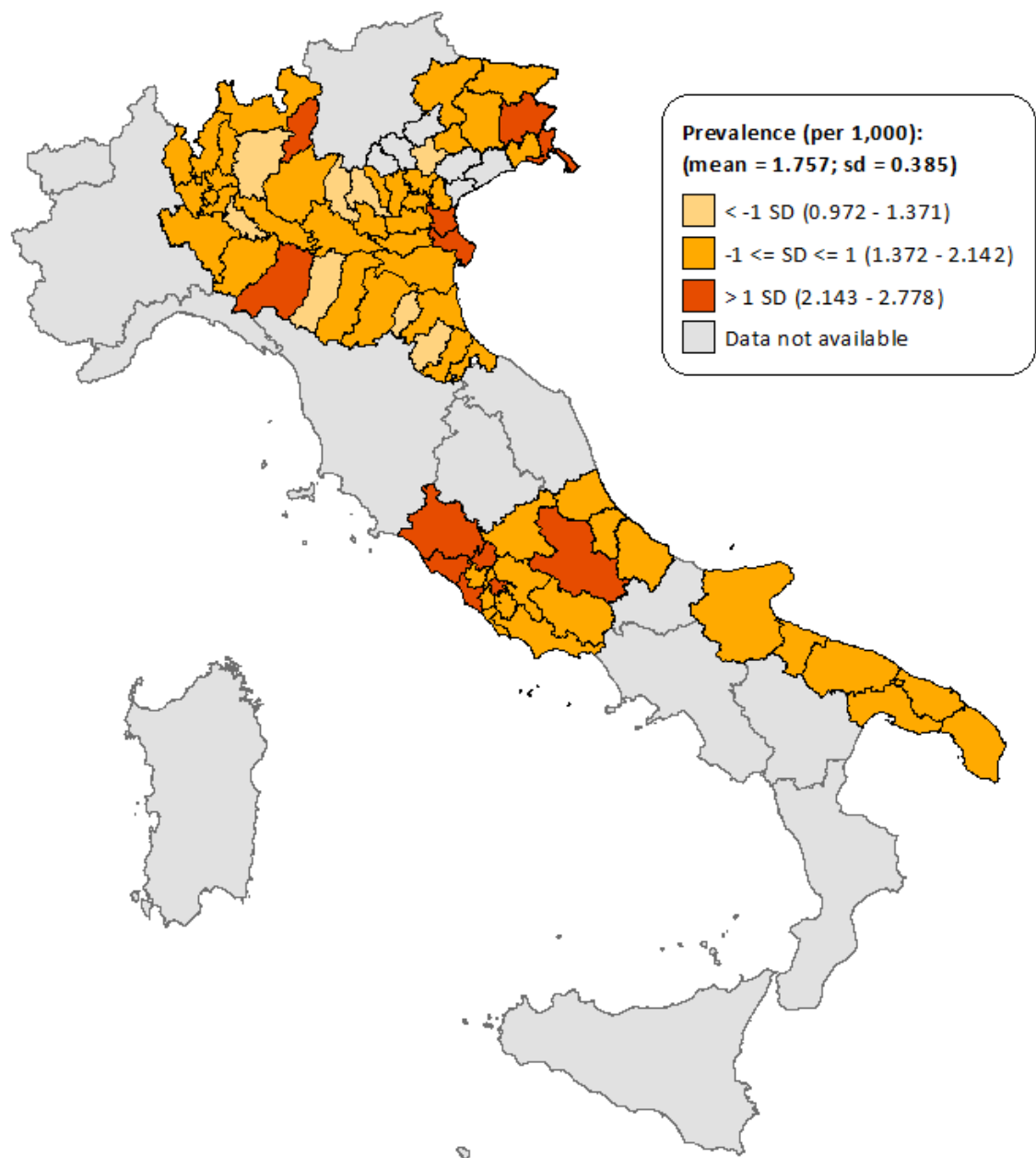
0-5		6-11		12-17	
Drug	*	Drug	*	Drug	*
<i>Trazodone</i>	0.310	Risperidone	3.31	Sertraline	8.77
Risperidone	0.240	Methylphenidate	2.12	Risperidone	7.70
<i>Escitalopram</i>	0.181	Sertraline	1.01	Fluoxetine	3.37
<i>Citalopram</i>	0.158	Atomoxetine	0.63	<i>Paroxetine</i>	3.30
<i>Sertraline</i>	0.135	Periciazine	0.36	<i>Escitalopram</i>	2.26
<i>Venlafaxine</i>	0.111	<i>Pimozide</i>	0.36	Aripiprazole	2.24
<i>Duloxetine</i>	0.100	<i>Amitriptiline</i>	0.34	<i>Citalopram</i>	1.78
<i>Paroxetine</i>	0.082	<i>Aripiprazole</i>	0.23	Methylphenidate	1.57
Periciazine	0.053	<i>Haloperidol</i>	0.20	Olanzapine	1.17
<i>Quetiapine</i>	0.041	Chlorpromazine	0.18	Atomoxetine	0.66

* x 10,000

b. Regional profile

During 2011, the prevalence of psychotropic drugs ranged from 1.56‰ (95% CI 1.50-1.62) in the Lombardy Region to 2.17‰ (95% CI 1.96-2.39) in the Friuli Venezia Giulia Region, Table 7. At the LHU level the prevalence ranged from 0.97 to 2.78‰, Table 7, Figure 5. The CV of regional prevalence ranged from 0.13 in the Friuli Venezia Giulia Region to 0.29 in the Abruzzo Region. The number of prescriptions per youth ranged from 3.87 in Emilia Romagna, to 5.36 in Abruzzo. The incidence was more homogenous and ranged from 0.86‰ (95% CI 0.78-0.93) in the Veneto Region, to 1.27‰ (95% CI 1.20-1.35) in the Lazio Region. The hospital admission rates ranged from 0.60‰ in Lazio (95% CI 0.55-0.65) to 3.83‰ (95% CI 3.54-4.11) in Friuli Venezia Giulia.

Figure 5 – Choropleth map of the participating regions and LHUs. The values of prevalence were categorized into three classes calculated on the basis of the mean±1 sd



Risperidone was the most prescribed psychotropic drug in five out of seven regions. The only two active substances that were among the 10 most prescribed in all regions were risperidone and sertraline. In fact, risperidone, along with methylphenidate and paroxetine, were among the 10 most prescribed active substances in six out of seven regions.

The Welch's ANOVA analysis found a significant difference between regions in the prevalence by LHUs ($F = 3.16$, $p = 0.03$). The post-hoc analysis found a significant difference

between the prevalence of Friuli Venezia Giulia and Emilia Romagna regions (mean difference= 0.57‰; 95% CI 0.01-1.12). There was no significant correlation between prevalence and prescription rates ($R_p=0.05$; $p=0.66$), latitude ($R_p=-0.10$; $p=0.42$), longitude ($R_p=0.17$; $p=0.16$), average annual income ($R_p=0.10$; $p=0.42$) or hospital admission rates ($R_p=0.21$; $p=0.08$).

c. Temporal trend

The overall prevalence of psychotropic drug prescription from 2006 to 2011 was stable, and no significant trend was found ($\chi^2_t= 0.001$ $p=0.97$). There was a slight increase in antipsychotic prevalence ($\chi^2_t= 32.4$; $p<0.001$) from 0.60 to 0.69‰, and a decrease in antidepressants prevalence ($\chi^2_t= 187$; $p<0.001$) from 1.26 to 1.02‰. An increase was observed in ADHD medication prevalence ($\chi^2_t= 1065$; $p<0.001$), from 0.01 to 0.19‰, Table 9.

Table 9 - Prevalence and incidence of psychotropic medicine prescriptions in youths <18 years, 2006 to 2011

	2006	2007	2008	2009	2010	2011	p-value
	N=4,569,190	N=4,641,857	N=4,688,005	N=4,752,154	N=4,991,496	N=5,019,564	
Antipsychotics							
Prevalence	0.60	0.62	0.65	0.65	0.65	0.69	<0.001
Incidence	0.28	0.32	0.31	0.31	0.30	0.32	0.04
Antidepressants							
Prevalence	1.26	1.22	1.14	1.16	1.03	1.02	<0.001
Incidence	0.92	0.89	0.81	0.84	0.72	0.70	<0.001
ADHD medications							
Prevalence	0.01	0.04	0.11	0.14	0.16	0.19	<0.001
Incidence	0.00	0.03	0.08	0.06	0.06	0.08	<0.001
Any psychotropic							
Prevalence	1.74	1.74	1.76	1.81	1.70	1.75	0.97
Incidence	1.15	1.18	1.14	1.15	1.02	1.03	<0.001

Values are expressed as per 1,000 children; (number of children).

The incidence of new psychotropic drug users decreased from 2006 to 2011 ($\chi^2_t=60,3$ p<0,001) from 1.15 to 1.03‰. The same trends were observed in the incidence of new

users considering antidepressants, while an increase was observed in antipsychotics and drugs for ADHD.

There was a significantly increasing trend in psychotropic drug prevalence in Friuli Venezia Giulia, from 1.68 to 2.17‰, and Veneto, from 1.30 to 1.57‰ (respectively $\chi^2_t=14.3$ and $\chi^2_t=31.6$; $p<0.001$), while a slightly decreasing trend was present in Emilia Romagna ($\chi^2_t=5.27$ $p=0.021$) with the prevalence shifting from 2.16 to 1.98‰. The prevalence observed in the other regions did not show significant trends.

The hospital admission rate decreased slightly ($\chi^2_t=5.30$ $p=0.02$) from 1.49 in 2006 to 1.44 in 2011.

4. Discussion

This is the largest pharmacoepidemiological study evaluating psychotropic drug prescription in the Italian paediatric population, including multiple regions and covering half of the Italian population of this age.

Considering the 2011 data, the overall prevalence found was very low compared to those from epidemiological studies in most other countries [26,79,81,82,90,94-107]. In particular, prevalence of prescription of stimulants in Italy were much lower than that of other regions of the world. Stimulants were prescribed to 0.19/1000 children less than 18 years in Italy, and to 42/1000 children in the United States who were commercially insured. Prevalence of prescription of other medications in other countries to children (<18 years) is shown in Table 10.

Table 10 - Prevalence (%) of antidepressants (AD drugs), antipsychotics (AP drugs), and ADHD medications observed in ≤ 18 years old in western countries in the last ten years. Data concerning Italian children are reported in bold characters.

Country	AD drugs	AP drugs	ADHD drugs
USA	27-38 (New England 2007-2010) ¹ 16 (Mid-Atlantic states, Medicaid, 2012)	7-26 (2007-2010) ¹ 49.5 (2008) 30.5 (2013)	42-77 (2007-2010) ¹
UK	11 (2012) 4.9 (2015) ³	0.77 (2005)	9.2 (2008) ² 7.4 (2008) ⁴ 5.11 (2013) ⁵
Germany	4.8 (2012) 2 (2012) 2.1 (2011)	3.2 (2012) 3.1 (2012) 2.6 (2011)	19.1 (2012)
The Netherlands	2.0 (2005) 6 (2012)	6.8 (2005)	21 (2007) ⁶
France	3 (2010)	3 (2010) 4.9(2013) ⁷	2 (2010)
Denmark	2.67 (2010) 10 (2012)	2.05 (2010)	7.29 (2010) 10 (2008-2012) ⁶
Iceland	n.a.	n.a.	12.5 (2007) 33 (2008-2012) ⁶
Finland	5.93 (2005)	n.a.	1.2 (2007) 5 (2008-2012) ⁶
Sweden	n.a.	n.a.	2.5 (2007) 12 (2008-2012) ⁶
Norway	7.0 (2010) 5.9 (2014)	1.9 (2014)	4.7 (2007) 14.8 (2014) 14 (2008-2012) ⁶
Canada	15.4 (2007)	7.4 (2008)	21 (2007) 38 (2011) ⁷
Ireland	2.61 (2008) ⁵	n.a.	8.63 (2011) ¹
Japan	4.2 (2008-2010)	8.0 (2008-2010)	3.0 (2008-2010) ⁵
Israel	n.a.	n.a.	49 (2011) ⁶
Italy	1.02 (2011)	0.70 (2011)	0.19 (2011)

¹ prevalence for commercially-insured patients (lower value) and Medicaid-insured patients (higher value)

² 6-12 years old

³ 3-17 years old

⁴ 13-17 years old

⁵ 0-15 years old

⁶ 6-17 years old

⁷ 1-24 years old

Several reasons for the different prevalence of psychotropic prescriptions between countries have been proposed in the literature, the most common of which are differences in policy, regulation, and access to mental health services [88,89]. Other important factors are cultural (i.e. perceived misuse of psychotropic medication in youths, possible adverse effects, etc..), but also include the role of non-pharmaceutical alternatives, and, ultimately, the uncertainty of indications (i.e. difficulty in deciding where to place cut-offs for the prescription of a drug) [89]. The observed, quite homogeneous and limited, prescription of psychotropic medications could be due to a generalised concern about psychotropic medications in children, at least in Italian parents [88]. For the same reasons, non-pharmacological treatments might be preferred in Italy, where drug therapy is reserved only to a small fraction of the children attending mental care services [27]. On the other hand, a study conducted in the Lombardy Region, showed that the majority of adolescents receiving antidepressant drugs were not followed by a child and adolescent psychiatrist, and this is clearly alarming [27].

A previous multiregional study that used a different database and sample population already analysed psychotropic drug prescriptions in Italian youths, in the 1998-2004 period [78]. By merging data from the two studies the prevalence of psychotropic medications was found to increase in 2001 and reach 3.08‰ in 2002 [78], to then decrease to 1.76‰ in 2006, and to afterward remain quite stable. After the statement about the increased risk of suicidal in adolescents receiving SSRIs, the amount of psychotropic drugs relevantly decreased. The plateau trend observed in the years afterwards is different from what was observed in other countries, where psychotropic prevalence, especially antidepressants, started to climb again, this fact is discussed further later on [80,82,94,100-105]. Even if we have no data to demonstrate this, we can speculate that the safety issue about SSRIs further increased the suspiciousness about paediatric psychotropic drug treatment and prevented the prevalence to reach the levels observed in the previous years like in other countries.

The analysis of prevalence by age and gender shows different utilization patterns among males and females, which somewhat reflect the differences in terms of prevalence of mental diseases, with antipsychotics and ADHD medications prescribed more in males at all ages, and antidepressants prescribed more in adolescent females. Although the amount of psychotropic drug prescriptions in Italian children is limited, a majority is represented essentially by antidepressant prescriptions for adolescent females.

Considering the single classes, there was a decreasing prevalence of antidepressants, and a large increase in the prevalence of drugs used for ADHD. The reasons behind the large increase in ADHD medications is that the marketing authorization of methylphenidate and atomoxetine in Italy was granted in 2007. The prevalence in 2011, however, is still very low compared to other countries [81-85,108]. The limited prescription of ADHD medications is partly due to the fact that in Italy the prescription requires strict diagnostic assessment and continuous monitoring [109,110]. Drugs can be prescribed by child psychiatrists with expertise in ADHD treatment, after a standardised diagnostic process [109]. It is also possible that the prevalence of ADHD might be lower than in other countries. In fact, in recent studies the prevalence of ADHD ranged from 0.5% [110], considering only those patients accessing child psychiatric services, to about 1% (surveys) [111,112]. Moreover, Italian youths with ADHD tend to be treated more frequently with non-pharmacological approaches, and, only in case of severe impairment, with a pharmacological treatment. A recent survey estimated that about 1 in 4 children with diagnosed ADHD receives drug therapy [109]. Furthermore, in Italy there are not external determinants that may increase pressure on drug prescription such as school, or insurance, like in other countries.

Despite their decreasing prevalence, antidepressants are still the most prescribed class of psychotropic medication, especially in adolescents. The negative trend observed could be partly explained by the fact that in Europe the warning concerning the higher risk of suicidal behaviour in adolescents treated with some SSRIs was issued in April 2005 [113], which was the beginning of our observation period. Nevertheless, the observed data are in contrast

with what is shown in other European countries concerning antidepressant prescription in youth. In fact, for example, in Denmark there was a linear increase in the prevalence from 1996 to 2010 [93], and in UK [114] and Germany [90] there was a decrease only in the years around the 2002-2006 period (and was very marginal in Germany), after which prevalence rose again. The overall prevalence observed in this study is twofold lower than that in Denmark and UK in the same years, and about five fold lower than the prevalence observed in Germany.

The most prescribed antidepressant was sertraline, which is approved for obsessive-compulsive disorder in children older than 6 years of age. The data are different from Germany, for example, where the most prescribed antidepressant in all age groups was fluoxetine [90].

In comparison with recent studies showing large increases in the use of antipsychotics in youths worldwide [93,115-118], a modest increase in the study period was observed. Risperidone was the most prescribed antipsychotic, as well as the most prescribed psychotropic medication in the overall population and in school-aged children. In Italy risperidone is approved for conduct disorder, and is used mostly to treat autism related symptoms, in particular aggressive behaviour.

Four out of the ten most prescribed psychotropic drugs were prescribed off-label by age: three SSRIs (paroxetine, escitalopram, and citalopram) and one antipsychotic (olanzapine). Besides these drugs, also pimozide and haloperidol are not approved in youths in Italy, amitriptyline is approved for adolescents older than 12 years of age, and aripiprazole for those older than 15. These drugs were, nevertheless, among the ten most prescribed in school-aged children. Similar results in terms of off label use were observed in other international studies [119-121].

When looking at the geographical distribution of psychotropic drug prescriptions no clusters were identified. At the regional level, the most relevant difference was between Friuli Venezia Giulia and the rest of the regions, and, when comparing the distribution of

prevalence at the LHU level by regions, only a tiny statistical difference was found. The prevalence of psychotropic drug prescriptions did not correlate with latitude or longitude, nor with annual income. On the contrary, a North-South trend and an inverse correlation between prevalence and annual income was found in studies evaluating the pattern of prescription of antibiotics and antiasthmatics [6,8].

In particular, when comparing the regional distribution of overall prevalence of drug prescription observed in a previous study [122] with the prevalence of psychotropic medicines no correlation is found. This fact suggests that psychotropic prescribing pattern is different from that of others medicines prescribed in youths. It is likely that local differences in cultural factors, prescribing attitude, and environmental setting play a less important role in psychotropic drug prescription compared to other, more widely used, drug classes. These facts strengthen the hypothesis of a more homogeneous, or differently distributed, prescribing attitude concerning psychotropic drugs. Since in this study the diagnoses corresponding to each prescription was not available, we compared the psychotropic drug prevalence and hospital admission rates for psychiatric disorders at the regional level in order to investigate a possible correlation. The correlation was not found, hence we could deduce that the regional differences observed in the epidemiology of severe psychiatric diseases alone may not explain the differences in drug prescriptions, but other factors may play a role.

Looking at the distribution of active substances by region, it was quite unexpected that only four active substances (risperidone, sertraline, methylphenidate, and paroxetine) are among the ten most prescribed in six out of seven regions, and only risperidone and sertraline are among the most prescribed in all the regions. This geographic variability in the choice of psychotropic medicines is particularly evident for SSRIs, and is probably due to prescriber attitude (e.g. medical specialty) and to local variability in the marketing of different active substances. However previous studies showed that in Italy about 3 out of 4 antidepressant prescriptions to children and adolescents are filled by GPs without the

supervision of a child and adolescent psychiatrist [27,91]. It is, therefore, likely that GPs prescribed to adolescents the same active substances they are used to prescribe in adults. It is striking that paroxetine, which is not approved for use in youths, is among the most prescribed active substances in six out of seven regions, while fluoxetine, which is approved for major depressive disorder in children older than eight years of age, is not.

The major strength of this study is the fact that it is a large multiregional study, and that the regions included were representative of different socio-demographic and geographic settings, and covered about half of the Italian paediatric population. Some limitation must be considered, however. We were able to include only seven regions and not the overall paediatric Italian population, however we included a representative sample of regions belonging to different geographic areas and with different socio-economic backgrounds. It would be plausible to state that in our sample the South of Italy is a bit under-represented, however the two regions included almost 40% of the overall South population.

Since we used drug prescription as a proxy of pharmacological treatment, it was not possible to assess if the drug was actually consumed by patients, and this is a limitation. However this limitation do not influence the results of the study, since its aim was to monitor prescribing, and not consumption trends. Another possible limitation is the fact that only reimbursed prescriptions were included, excluding out-of-pocket dispensation and those filled by private practices. However, these phenomena are likely to be negligible for reimbursed drugs. Anxiolytics, sedatives, and hypnotics were not retrieved in the database used for this study, leading to an underestimate of the overall prevalence. However, this class of drugs should not account for a large proportion of psychotropic drugs in children, as shown in a recent Danish study [93]; the underestimate should therefore be marginal. Nevertheless, the prevalence of each single class of psychotropic drugs is lower in Italy than in other countries, as previously described. Information on the diagnosed diseases for which a drug was prescribed was not available, and precluded any evaluation of the appropriateness of prescribing. This is, however, an intrinsic limitation of most

pharmacoepidemiological studies using prescription databases. Some data were not available concerning the Abruzzo Region, as described in the methods section, leading to the exclusion of youths living in the Abruzzo Region for the temporal trend analyses.

5. Conclusions

In this large pharmacoepidemiological study including about half of the Italian youth population, the prevalence of psychotropic drugs observed was substantially lower than in other countries and remained stable during the observation period. No significant clusters were found in the geographic distribution of psychotropic drug prescriptions, differently from what was observed for other classes of medicines, showing a quite uniform, limited prescription of psychotropic medications.

VI. Quality of drug prescribing in paediatrics

A. Review of Italian primary care paediatricians identifies 38 commonly prescribed drugs for children

1. Introduction

Children are one of the patient populations most exposed to drugs [3]. Wide qualitative and quantitative differences have been documented in the international literature, and within countries and regions, that are most likely not due to differences in the epidemiology of diseases [6,12,20]. A wide range of drugs is prescribed for Italian paediatric patients, but there are only a limited number of active substances that are commonly prescribed by the majority of FPs [123]. This is due to differences in prescribing attitudes and different geographic and socio-cultural settings, as well as to the marketing of me-too drugs, which are compounds with the same mechanism of action as an existing, approved chemical entity. These drugs, in most cases, do not bring real advantages to patients when compared to the standard treatments [124]. In developed countries the availability of a large amount of active substances, often with overlapping indications, may lead to confusion and difficulties in choosing the most suitable pharmacological treatment [125].

The World Health Organization (WHO) defines essential medicines as those needed in a basic healthcare system. Such drugs should be able to fulfil essential medical needs and are included in the EMLC by considering prevalence of diseases, efficacy, safety and cost effectiveness [126,127]. The WHO estimated that, even with large differences among countries, half of the prescriptions filled worldwide could be inappropriate [128]. It has been demonstrated that clinicians often have to choose between a very large number of drugs for a certain condition and that these complex decisions reduce the possibility of making a rational choice and increase the risk of inappropriate prescriptions [129,130].

Prescribing based on a defined list of the best drugs available, excluding less effective and more toxic drugs, could reduce the rates of inappropriate prescriptions [131]. However, the EMLC represents a minimal list of drugs needed for priority conditions at the worldwide

level, and is thus not applicable to any specific country, since countries may have different medical needs and priorities. An acknowledged formulary of drugs for children is still unavailable at the European level and the most used paediatric formulary is the British National Formulary for Children.

The aim of this observational study was to identify a list of drugs commonly prescribed by a reference group of Italian FPs during their daily clinical practice. This group has been involved in educational initiatives concerning care and appropriate prescribing for years.

2. Methods

a. Data source

The survey group comprised of 64 FPs, who worked in the northern part of the Lombardy Region of Italy and each cared for a similar number of patients. The paediatricians were a small group of paediatricians near Milan part of an Italian cultural association of paediatricians called ACP known by our laboratory since a decade for their initiatives on enforcing guidelines on the appropriateness of prescribing.

The period of observation was from 2 April to 1 June 2012. The participating FPs systematically recorded, in electronic medical records, all the cartons of drugs prescribed in the primary care clinic, indicating those recommended by a specialist (S).

The trade names of the drugs and the number of cartons prescribed were collected using two different software programmes (Junior bit[®] and Infantia 2000[®]), which were those commonly used by the FPs for electronic case reports. Drugs were subsequently classified according to the Anatomical Therapeutic Chemical classification system, aggregated into therapeutic subgroups and divided according to whether the cost was reimbursed: class A drugs reimbursed by the NHS, class C drugs not reimbursed by the NHS and over-the-counter (OTC) drugs.

The outcome measures were the number and percentage of cartons prescribed for each active substance and therapeutic subgroup. For each active substance we calculated the percentage of prescribers, defined as the percentage of FPs prescribing at least one carton of the drug during the study period, and the percentage of prescriptions based on the recommendation of a specialist.

When prescriptions were recorded on the INFANTIA 2000® software, it was possible to distinguish between branded and generic drugs and to identify the formulation. Drug formulations were divided into oral use, which comprised tablets, capsules, and oral solution/suspensions, and rectal, topic, injectable and inhalator use.

Drugs included in the list of commonly prescribed drugs were those: 1) prescribed by 50% or more of the FPs following their own clinical assessment; 2) for which $\geq 50\%$ of cartons were prescribed according to the recommendation of a specialist and prescribed by $\geq 25\%$ of FPs. Aggregated and anonymous data were provided and, therefore, ethical approval was not required.

3. Results

A total of 381 active substances were prescribed and these were classified into 70 therapeutic subgroups. Of these, 183 were classified as class A, 107 as class C and 91 as OTC. The 10 most prescribed active substances covered more than 60% of the cartons (Table 11).

Table 11 – List of medicines prescribed by ≥ 50% of FPs and percentage of prescriptions

Active substance	Prescriptions		Prescribers	
	n.	(%)	n.	(%)
amoxicillin	8.879	25.1	64	100.0
salbutamol	1.516	4.3	64	100.0
amoxicillin clavulanate	3.255	9.2	63	98.4
cetirizine	3.199	9.0	63	98.4
betamethasone	1.075	3.0	63	98.4
beclometasone	1.224	3.5	60	93.8
oral aciclovir	688	1.9	60	93.8
fluticasone	536	1.5	59	92.2
clarithromycin	653	1.8	57	89.1
azithromycin	770	2.2	54	84.4
budesonide	335	0.9	53	82.8
ophthalmic tobramycin	322	0.9	53	82.8
levocetirizine	464	1.3	52	81.3
valproic acid	624	1.8	49	76.6
cefixime	495	1.4	49	76.6
montelukast	322	0.9	49	76.6
ibuprofen	311	0.9	49	76.6
oxatomide	181	0.5	48	75.0
paracetamol	638	1.8	43	67.2
cefpodoxime	447	1.3	43	67.2
cefaclor	358	1.0	42	65.6
flunisolide	277	0.8	42	65.6
cholecalciferol	734	2.1	41	64.1
macrogol	135	0.4	41	64.1
mebendazole	111	0.3	40	62.5
desloratadine	192	0.5	38	59.4
prednisone	174	0.5	38	59.4
salmeterol combinations*	158	0.4	38	59.4
betamethasone+gentamycin derm.	146	0.4	36	56.3
ophthalmic ketotifen	133	0.4	36	56.3
paracetamol combinations †	72	0.2	35	54.7
mometasone	138	0.4	32	50.0
iron compounds (III)	85	0.2	32	50.0
other	6,734	19.0	/	/
Total	35,381	100.0	/	/

grey cells = non reimbursable drug

* other drugs for obstructive airway diseases

† excluding psycholeptics

Each FP prescribed a median of 52.5 (25-104) active substances. A total of 35,381 cartons of drugs were prescribed during the observation period: 30,288 (85.6%) were class A, 2,582 (7.3%) were OTC, and 2,511 (7.1%) were class C.

Systemic antibiotics (43.8% of the cartons), anti-asthmatics (12.9%) and antihistamines (11.8%) were the most prescribed classes. The most prescribed active substances were: amoxicillin (25.8% of cartons), amoxicillin clavulanate (9.2%), and cetirizine (9.0%). The number of active substances in the most prescribed therapeutic subgroups, is reported by percentage of prescribers (Table 12).

Table 12 – Distribution of active substances among therapeutic subgroups ordered by percentage of prescribers. Only classes with at least one active substance prescribed by \geq 50 % of FPs were included.

Therapeutic subgroup	Active substances			
	<50%	50-74%	\geq 75%	total
antibiotics (J01)	22	2	5	29
anti-asthmatics (R03)	6	2	5	13
antihistamines (R06)	6	1	3	10
corticosteroids (H02)	3	1	1	5
antiepileptics (N03)	12	0	1	13
ophthalmologicals (S01)	31	1	1	33
NSAIDs (M01)	5	0	1	6
antivirals (J05)	1	0	1	2
dermatologic corticosteroids (D07)	16	2	0	18
analgesics (N02)	2	2	0	4
vitamins (A11)	6	1	0	7
<i>other</i>	238	3	0	229
total	348	15	18	381

The formulation was available for a total of 11,186 cartons of drugs (31.6% of the total), prescribed by 17 FPs. The percentages of class A, class C and OTC cartons in this prescription subgroup were similar to those observed in the overall sample. The most

prescribed cartons were oral formulations (76.6%). In particular, solutions/suspensions accounted for 54.8%, tablets/capsules for 21.8%, inhalors for 12.1%, topical drugs for 6.4%, injectable drugs for 4.0% and rectally administered drugs for 0.9%. When we looked at the five most prescribed active substances, we found that the number of different medicinal products prescribed ranged from three for betamethasone to 34 for amoxicillin clavulanate and that only one out of three and five out of 34 of these formulations, respectively, were prescribed by 50% or more of the FPs.

In total, 30% (3,361) of the cartons were generic. The rate of generic prescriptions for the three most prescribed classes of drugs, was 54.0% for antibiotics, 25.5% for anti-histamines and 2.4% for anti-asthmatics. Among the five most prescribed drugs, amoxicillin had the highest rate of generic prescriptions (68.5%), followed by amoxicillin clavulanate (47.1%), cetirizine (30.0%), and salbutamol (5.9%). There was a high variability of generic use among FPs, ranging from 3.2% to 55.6% of cartons prescribed.

a. Prescriptions recommended by the specialist

During the study period, 57 (89.1%) of the FPs prescribed at least one drug recommended by a specialist and a total of 175 active substances, belonging to 52 therapeutic subgroups, were prescribed. Of these, 36 drugs were prescribed exclusively based on the recommendation of specialists and the most commonly prescribed were: carbamazepine (88 cartons), levocarnitine (12), and zonisamide (11).

The number of cartons recommended by specialists was 2,903 (8.2%) and the most recommended classes were antiepileptics (75.5% of the cartons), pituitary and hypothalamic hormones and analogues (62.4%), drugs used in diabetes (59.5%) and thyroid therapy drugs (58.9%). Valproic acid (382 cartons) and somatropine (246) were the most recommended active substances in terms of number of cartons prescribed.

b. List of commonly prescribed drugs

According to the defined criteria, a list of 38 commonly prescribed drugs belonging to 16 therapeutic subgroups and covering 83.1% of prescriptions was identified. Of these, 33 were prescribed by 50% or more of the FPs and five were mainly prescribed following the recommendation of a specialist (Table 13).

Table 13 – List of shared medicines identified by the predefined criteria. Therapeutic subgroups are ordered by number of packages.

Therapeutic subgroup	Active substances
antibiotics	amoxicillin, amoxicillin clavulanate, cefaclor, cefixime, cefpodoxime, azithromycin, clarithromycin
anti-asthmatics	salbutamol, salmeterol combinations, beclometasone, budesonide, flunisolide, fluticasone, montelukast
antihistamines	oxatomide, cetirizine, levocetirizine, desloratadine
corticosteroids	betamethasone, prednisone
antiepileptics	carbamazepine (R), valproic acid (R), levetiracetam (R)
ophthalmologics	tobramycin, ketotifen
vitamins	cholecalciferol
analgesics	paracetamol, paracetamol combinations excluding psycholeptics
antivirals	aciclovir
dermatological corticosteroids	mometasone, betamethasone and gentamicin
pituitary and hypothalamic hormones and analogues	somatropine (R)
anti-inflammatories	ibuprofen
antihelmintics	mebendazole
drugs for constipation	macrogol
drugs used in diabetes	insulin* (R)
antianemics	iron compounds (III)
thyroid therapy	levotiroxine (R)

* and analogs

(R) ≥ 50% of packages recommended by a specialist

4. Discussion

This observational study evaluated the profile of drugs prescribed during daily clinical practice by a group of FPs, who has been involved in healthcare initiatives for a number of years. Over 85% of the cartons prescribed were reimbursable. This data is different from a previous study in the South of Italy that analysed a sample and found that more than 30% were non-reimbursable drugs [132]. The current study shows that, despite the fact that non-reimbursable drugs represented more than half of the active substances prescribed, only seven of them were commonly prescribed in clinical practice and these were paracetamol, ibuprofen, mometasone, betamethasone plus gentamycin, tobramycin, ketotifen and macrogol. The high percentage of reimbursable prescriptions indicates that the profile emerging from studies using administrative databases of reimbursed prescriptions is quite representative of the overall prescribing practice [3,20].

This study highlighted that the diseases requiring more drug prescriptions following the recommendation of a specialist were chronic illnesses, such as epilepsy, diabetes and a number of endocrinological conditions. By using the same approach, on the basis of the prescription profile, the diseases that were treated mainly by FPs were infections, asthma and dermatological, gastroenterological and ophthalmological conditions. The list of the therapeutic areas identified could be used to create a widely acknowledged formulary of common paediatric drugs that reflects FPs' practices.

The most prescribed active substances were antibiotics, anti-asthmatics and anti-histamines, as observed in other pharmacoepidemiological studies in children [20,65,133]. A 1998 study on paediatric prescriptions in southern Italy showed similar results concerning drug classes, with a higher average number of active substances prescribed by FPs [65]. Antibiotic prevalence was high compared to that of most of the other European countries, but is similar to reports in the literature concerning Italian children [3,6,12,20,22,134].

Different medicinal products containing the same drug were used by FPs. The different attitudes may be due to the specific preferences of the FP, the influence of marketing and the different palatability of formulations [135].

The percentage of generic drugs observed in this study (30%) was low when compared with those of other European countries (70%) [134], but higher than the percentage in a survey on Italian FPs (13.5%)[136]. This is probably due to the fact that FPs involved in educational initiatives may be more likely to prescribe generic drugs [22]. However, the data in the current study showed that even in a small group of FPs the attitudes towards generic prescribing differed widely, indicating that personal preferences exerted a strong influence.

By using the predefined criteria, we identified a total of 38 active substances necessary to fulfil the most relevant clinical needs in the primary care paediatric setting. These data confirm the fact that a relatively small number of drugs are used frequently. Of these drugs, 14 (37%) were included in the EMLC. The difference between our list and the EMLC list is partly due to different health needs, priorities and settings, in other words local versus global. For example, macrogol is the drug of choice recommended by the NICE, which provides the UK NHS with advice on drugs [137], but it is excluded from the EMLC and constipation is certainly not a priority condition in countries with scarce resources.

Besides the incidence and prevalence of diseases, other reasons for the differences between the two lists may include high treatment costs, because treatments like somatropine are unlikely to be affordable in low-income countries. In addition, regulatory or marketing reasons may influence views on how essential drugs are. Betamethasone, for example, was prescribed by 63 of the 64 FPs in our study but is not included in the EMLC. The WHO, in fact, suggests that prednisolone should be the first choice oral corticosteroid. International guidelines on the management of childhood asthma state that oral corticosteroids should be used in acute exacerbations when there is a suboptimal response to β 2-agonists [138,139]. In Italy, however, this recommendation is often not followed and these drugs are used mostly to improve symptoms of common URTI, even if there is no

evidence of efficacy [140]. Betamethasone has a very low cost in Italy and the formulation, small dispersible tablets, means that it can be administered to very young children. Therefore, this drug is preferred to other oral corticosteroids for asthma and wheezing therapy.

Among the 38 selected drugs, duplications observed in previous studies still persist [123]. The presence of four different inhalation corticosteroids (beclometasone, flunisolide, budesonide and fluticasone) and two third-generation cephalosporins sharing the same posology (cefixime and cefpodoxime) is unlikely to be due to different levels of efficacy. Finally, the adoption of a European formulary of paediatric drugs would be helpful in promoting a more rational and homogeneous use of drugs in children within countries [141]. The rational use of drugs in children is an area of research that has not been sufficiently studied and there is a need for interventions to improve it [1]. A formulary of the most useful and effective medications for the most common paediatric diseases would represent a concrete step towards implementing the rational use of drugs in children.

Our study has some limitations. It is possible that the list of drugs we identified is not applicable to other FPs and geographic settings. In fact, the FPs had similar educational levels and motivation and were thus not representative of a broader setting, such as a regional or national one. Furthermore, since the role of the FP does not exist everywhere, the results may not be applicable to other countries with different systems of paediatric care, where GPs treat most children. The observation period lasted eight weeks and a longer duration could have identified additional drugs. However, the results are quite similar to observations from other paediatric studies [134]. Unfortunately, we were not able to collect information concerning the drug dosages and the diseases diagnosed. Nevertheless, by looking at the qualitative and quantitative prescription profile, the study provides useful insight into the most prominent clinical needs observed in this paediatric population.

5. Conclusions

In conclusion, this study allowed the identification of a list of drugs commonly prescribed by a group of FPs involved in healthcare initiatives for many years. This shows that 38 drugs would be sufficient to treat the most common childhood diseases in this sample of patients. Identifying this list of commonly prescribed drugs by this group of experienced FPs could provide a good starting point for creating a minimal paediatric formulary that addresses the most common clinical needs in the primary care setting.

B. Generic antibiotic prescribing in paediatrics

1. Introduction

A generic drug is defined as a medicinal product that has the same qualitative and quantitative composition in active substance and the same pharmaceutical form as the originator. In Italy, when a medicinal specialty is not protected by patent anymore, generic drugs are marketed with a 20 to 80% discount in price in respect to the originator. Thus, the marketing of generic drugs causes significant savings to the NHS, because the new reimbursed price correspond to that of the generic formulation. At the same time, the use of generic drugs instead of the brand name alternatives may cause some savings also for the citizens. In fact in Italy, if a generic exist for the drug that has been prescribed, the drug is fully reimbursed by the NHS only if the patient is willing to buy the generic. If the patient is willing to buy the brand name formulation of the drug, then a co-payment is due.

Generic drugs market is very large in the UK, Denmark, and Germany, representing about 70% of the cartons sold and about 30% of the expenditure, and generating 13 billion euros of savings (35 billion euros if considering the entire EU-27)[142]. In USA these percentages reached 80% in volume and 20% in expenditure, while in Italy generic drugs represent less than 14% in volume, and 7% in expenditure (about 300 million euros) [143]. Despite some improvements in the last few years, generic drugs prescribing continues to be limited in Italy in respect to other European countries and USA [134]. This difference may be due to differences in legislation, cultural factors, and prescribing attitudes.

Data concerning generic prescribing in paediatrics are scarce. One study conducted in the USA in 2002 reported that in under 18 years old about 41% of the overall prescriptions were generic drugs [144]. The percentage of generic drugs was higher in analgesics, antiasthmatics, and antibiotics (almost 70% of the total). Nowadays, also in paediatrics, the prescribing of generic drugs is scarce in Italy. A survey on 303 FPs in 2011 revealed that about 29% of the participants believed that generics may contain a lower quantity of active

substance compared to the originator [137]. The lack of bioequivalence study in children, different excipients, and palatability were indicated as the major issues of generic formulations. The FPs included in this study treated with generic drugs less than 20% of their patients [137]. An analysis of the prescription database of the Lombardy Region in 2005 estimated that 41% of children 6 to 13 years old treated with amoxicillin received at least one generic formulation of this drug [145].

Antibiotics are the most prescribed drugs in children and adolescents, and they represents 54% of the out of hospital expenditure for drugs in Italy [3,4]. The aim of this study was to evaluate generic antibiotics prescribing in paediatrics in the Lombardy Region, and to investigate some of the possible determinants.

2. Methods

a. Data Source

The data source was the Lombardy Region's database, which is routinely updated for administrative and reimbursement reasons. The database stores all community (i.e. outside hospital) prescriptions reimbursed by the NHS. Data were managed anonymously. Prescribed drugs were classified according to the Anatomic Therapeutic Chemical (ATC) classification system. Antibiotics were defined as all drugs belonging to the J01 ATC subgroup. Medicines were considered generic if they were marketed with the INN of the active substance.

b. Study population

The population included was composed of all children/adolescents <13 years old resident in the Lombardy Region, (1,276,932 children/adolescents and 1253 FPs). 15 LHUs were included in the study. The sample size of each LHU varied from 12,644 to 160,744 children. The population was divided in three groups of age: <1 year old, 1-5 years old, and 6-13 years old.

c. Measures and analysis

- Prevalence, as the percentage of resident children with at least one prescription in one year of observation;
- percentage of treated children, as the percentage of children with at least one prescription of a certain active substance divided by the children treated with antibiotics;

The association between antibiotic prevalence and the percentage of children treated with generic alternatives in the 15 LHUs was evaluated by using the non-parametric Spearman rank correlation test.

With the aim to evaluate the FPs' prescribing attitude in respect to generic drug prescription, FPs were classified into low, mean, and high prescriber on the basis of the number of antibiotic prescriptions per patient. A low prescriber showed a mean number of antibiotic prescriptions per patient equal to $\bar{y} - \text{sd}$ (lower than 0.72), a mean prescriber to $\bar{y} - \text{sd} < \bar{y} < \bar{y} + \text{sd}$ (0.72 to 1.5), and high prescriber to $\bar{y} > \bar{y} + \text{sd}$ (higher than 1.5). The percentage of generic antibiotic prescriptions was compared among the three groups of FPs through the non-parametric Kruskal-Wallis test, because the distribution of data was not normal, and the ANOVA test could not be used appropriately. The Wilcoxon signed-rank test was used to compare the generic prescription rate in the different groups of prescribers. The χ^2 for trend was used in order to compare the percentage of children treated with a generic formulation in the different age strata. A p-value < 0.05 was considered statistically significant.

3. Results

In 2008, 74 antibiotics corresponding to 813 medicinal specialty were available in the NPF. Of these, 339 tablets and capsules, 338 injectables, 136 suspensions for oral use were retrieved. For 39 active substances, corresponding to 611 medicinal specialty, a generic formulation was available. Cephalosporins (13 active substances), and penicillins (9 active substances) were the most represented class.

During 2008, 62 different antibiotics were prescribed to 590,940 children (46%) for a total of 1,337,236 prescriptions. Prevalence of antibiotic prescriptions was higher in boys than in girls (52 vs 48%), and reached the maximum value in children 1 to 5 years old (62%), decreasing to 39% in those 6 to 13 years old.

79% of the overall antibiotic prescriptions concerned antibiotic that had generic formulations available on the market (i.e. the patent expired). Generic prescriptions were 37% of the antibiotic with expired patent, and 29% of the overall antibiotic prescriptions.

The most prescribed formulations were oral suspensions that represented 88% of the antibiotic prescriptions. 86% (n = 509,825) of all the children treated with antibiotics received at least one antibiotic with expired patent. The 47% of these children (n = 239,781) received at least one generic antibiotic.

There were no gender differences in the prescription of generic antibiotics. The percentage of prescription of generic antibiotics decreased at increasing age: from 47% of children less than 1 years old, to 31% in those 6 to 13 years old ($\chi^2= 18.753$; $p < 0.001$). The most prescribed antibiotic was amoxicillin-clavulanate (40% of treated children), followed by amoxicillin (22%), and clarithromycin (10%). The 10 most prescribed antibiotics represented 97% of all the prescriptions for antibiotic drugs. Six of the ten most prescribed active substances had an expired patent: amoxicillin clavulanate, amoxicillin, clarithromycin, cefaclor, ceftriaxone, and cefuroxime. For these antibiotics generic paediatric formulations were available, with the exceptions of cefuroxime and ceftriaxone.

Table 14, shows the data concerning the four most prescribed antibiotics with expired patent. The percentage of prescription of generic antibiotics was 37%, from a minimum of 6% (clarithromycin) to a maximum of 72% (amoxicillin).

Table 14 – Data concerning the four most prescribed antibiotics with expired patent in terms of generic drug prescription

active substance	prescriptions* (n)	patent expiration (year)	medicinal specialties* (n)		generics (%)	
			total B/G	paediatric formulations (B/G)	treated children n	prescriptions
amoxi-clavulanate	552,984	2006	10/65	6/6	31.5	26.7
amoxicillin	283,769	1996	7/40	1/6	71.9	71.5
clarithromycin	120,360	2008	12/22	6/6	7.4	6.3
cefaclor	84,889	2002	7/35	5/17	37.2	34.6
other	50,422	-	54/100	3/17	28.5	28.0
total	1,062,424	-	90/262	21/52	40.4	37.0

*Prescriptions concerning active substances with expired patent, B brand name formulation, G generic name formulation

a. Prevalence and determinants

The prevalence of antibiotics varied from 37 to 52% in the 15 LHUs. The percentage of prescription of generic antibiotic was the lowest in the Sondrio LHU (12%) and the highest in Como LHU (48%). The percentage of children receiving generic amoxicillin followed the same trend ranging from 25% in Sondrio LHU, to 83% in the Milano and Como LHUs. A correlation between the antibiotic prevalence of prescription and the percentage of children treated with generic antibiotics was not found at the LHU level ($R_s = 0.19$; $p = 0.49$).

The proportion of generic drugs was higher in FPs prescribing less antibiotics to their patients, Table 15. The generic antibiotic prescription rate was lower in high prescribing FPs compared to the low prescribing FPs ($z = 2.44$; $p = 0.015$), and compared to the mean prescribing FPs ($z = 2.77$; $p = 0.005$).

Table 15 – Comparison of the proportion of generic prescriptions among different groups of paediatricians in respect to quantity of antibiotics prescribed

Prescriber	N	Generic prescription (% proportion of children)	
		Range	mean \pm DS
Low	167	0.0 – 78.5	39.4 \pm 20.3
Mean	842	1.5 – 88.3	39.1 \pm 21.6
High	169	2.9 – 84.5	34.4 \pm 22.8
Total	1,178	0.0 – 88.3	38.5 \pm 21.6
<i>p-value</i> ¹		0.015	

1. Kruskal-Wallis test

4. Discussion

This study is the first comprehensive analysis of generic antibiotics in paediatrics in Italy on a large pharmaceutical database. Despite being limited to the antibiotic class, the analysis is quite representative of the prescribing profile, because these drugs are the most used medicines in children. Furthermore there are a large number of available generic formulations of antibiotic on the paediatric market, and, as confirmed by a survey [137], antibiotics are the most commonly prescribed drugs as generics.

The antibiotic prescription profile observed in this study is similar to that previously described in the Lombardy Region and in other Italian regions, and further confirm the importance of the geographical determinant, and the higher prevalence in Italy compared to other north European countries [3,4,6]. The reasons for this difference are multiple: socio-cultural, economic, in the organisation of health systems, and in the physicians' prescribing attitude.

Generic antibiotic were scantily prescribed in this analysis. Despite the fact that for 6 out of 10 of the most prescribed antibiotics in children generic drugs were available on the market, only 37% of the prescriptions were represented by generic antibiotics, with wide differences among geographic areas and FPs. It is remarkable that only for amoxicillin the

generic formulations were prescribed more than the brand name ones. For amoxicillin-clavulanate, the most prescribed drug in Italy in children, generic prescriptions represented only 27% of the total, while in the case of clarithromycin the proportion of generic formulations prescribed was negligible (6%). These differences may be due only in part to the scarce availability of generic paediatric formulations, or to the period immediately after the patent expiration. In the case of clarithromycin, the patent expired in 2008, and this could explain the very low prescription rate of generic formulation of this drug. Nevertheless the very low prescription rate of generic formulations of cefaclor is not justifiable neither by patent expiration nor by the lack of availability of paediatric formulations. In fact cefaclor patent expired in 2003 in Italy, and 17 generic paediatric formulations were available.

The proportion of children receiving a generic formulation of antibiotics decreased with increasing age. This was probably due to the fact that amoxicillin, the antibiotic most prescribed as generic formulations, is the most prescribed antibiotic especially in the youngest children, due to the epidemiology of acute otitis media. The prescription rate of generic amoxicillin increased compared to 2005 in a similar population, from 41 to 72% [4]. This is encouraging and it confirms a trend in a more favourable prescribing attitude towards generic antibiotics in FPs. However, wide differences at the local level exist regarding the generic prescription rates, with a fourfold difference between the LHU with the lowest and the highest values. These differences are not associated with the qualitative profile of antibiotic prescriptions, since they persist also when considering only amoxicillin alone. Moreover, a correlation between antibiotic prevalence and the prescription rate of generic formulations was not found. This result seems to indicate that not necessarily the more “virtuous” LHUs in terms of low prevalence of antibiotic prescribed more generic formulations. In this regard the Sondrio LHU is emblematic: even being a geographic area that has a low prevalence of antibiotic prescription, the prescription of generic antibiotic is rare.

High prescribers were more likely to prescribe less generic antibiotics compared to low prescribers. Most likely this was due to qualitative differences in the prescription profile since amoxicillin has the highest prescription rate of generic formulations and other second choice antibiotics like cefaclor and clarithromycin are rarely prescribed as generic formulations.

5. Conclusions

The differences among different settings and physicians highlighted the need for educational interventions for prescribers and citizens concerning the use of generic medicines. In order to be effective these interventions should be part of a more broad task of improving rational use of drugs in paediatrics. Furthermore these interventions should be undertaken at the local level, especially where generic drug prescriptions is still rare.

C. Comparing recurrent antibiotic prescriptions in children treated with a brand name or a generic formulation

1. Introduction

According to the EMA a generic drug is a medicinal product having the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated to be within acceptable predefined limits [146]. Such limits are represented by the AUC and AUC_{∞} values ranging from less than 20% to more than 25% of the brand name drug values (CI 90% 0.8–1.25). A study on food interaction must be performed for oral drugs, as well as a study on palatability if there is a paediatric indication [146]. Such studies allow the marketing authorisation for the generic product.

Concerning the effectiveness of generic drugs, scepticism has arisen from both the consideration that the efficacy of generic drugs does not need to be proven in order for them to be authorised, and from unproven anecdotal reports of non-effectiveness [147,148]. One of the drug classes receiving attention due to such anecdotal reports, often fostered by marketing campaigns organised by brand name drug producers, is antibiotics. Antibiotics are the most used drug class in children, thus effectiveness is very relevant in this population of patients. In fact, generic antibiotics are less costly than the trade-name products and their increased use generates significant savings for both the patients and prescribers, without compromising therapeutic benefits [22,149].

A number of post marketing studies have looked at bioavailability of generic antibiotics compared with the originators, showing generally favourable results [150-155]. Only a few studies reported that generic tablets are sometimes not comparable in vitro to the originator product [150] or do not reach bioequivalence [151]. Failing to demonstrate bioequivalence because the confidence interval is slightly larger than allowed, however,

does not demonstrate lack of clinical effectiveness [152]. Moreover, most post-marketing studies demonstrated bioequivalence in clinical trials [153-155].

Concerning clinical effectiveness, post-marketing clinical trials are scarce, but showed no difference in clinical outcomes when comparing generic and brand name antibiotics [155,156].

Different paediatric formulations of antibiotics can have a substantially worse palatability profile, thus decreasing children's adherence and possibly increasing therapy failure rates [136,157]. Nevertheless, a clinical trial study failed to show significant differences in the compliance to oral suspension antibiotics when a brand name or a generic was given [158].

In this context, the aim of this study was to investigate the rate of recurrent prescriptions and hospital admissions as proxy of therapeutic failure in outpatient children receiving a generic/brand name antibiotic prescription by using a pharmacoepidemiological approach. The main goal of the study was to indirectly compare the clinical effectiveness of brand name and generic formulations of the same active substance in the real setting by using prescription data routinely collected for administrative reasons.

2. Methods

a. The reference price system

In Italy, the RPS was implemented in 2001. Under the RPS, the NHS reimburses the lowest price among the prices of off-patent pharmaceuticals with equal composition in active ingredients, with the same pharmaceutical form, method of administration, number of units and dosage. If patients refuse the substitution of a medicine with a generic alternative, the difference is paid by patients.

b. Data source

The data source was the Lombardy Region's database, which is routinely updated for administrative and reimbursement reasons. The database stores all community (i.e. outside hospital) prescriptions reimbursed by the NHS. Data were managed anonymously. Prescribed drugs were classified according to the Anatomic Therapeutic Chemical (ATC) classification system. Antibiotics were defined as all drugs belonging to the J01 ATC subgroup.

The population included was composed of all children/adolescents <18 years old resident in the Lombardy Region, a large Italian region located in the North of the country (1,669,856 children/adolescents in 2010). The chosen observation period was from 1 February to 30 April 2010.

Prescriptions were subsequently divided into index and recurrent prescriptions.

An index prescription of an antibiotic was defined as any antibiotic prescription that occurred during the observational period not preceded by a prescription in the previous 28 days (for a single child). A recurrent prescription was defined as an antibiotic prescription occurring from 1 to 28 days after an index prescription (for a single child). The month of May was considered a post-observational period during which only recurrent prescriptions were considered (included if a child received an antibiotic prescription in the previous 28 days). Children receiving more than four prescriptions during the observational period were excluded since they were more likely suffering from a chronic illness. Since a sufficient amount of children treated with a generic antibiotic was needed to compare recurrent prescription in the generic vs brand name groups of children, only prescription of the 4 antibiotic with a paediatric generic formulation available since at least two years were considered for the analyses (amoxicillin, amoxicillin clavulanate, cefaclor, and clarithromycin).

c. Therapy switch

In order to characterise the recurrent prescriptions, for each active substance and for both generic and brand name formulations, the percentage of therapy switch was calculated in terms of: percentage of different classes and active substances prescribed during the recurrence and percentage of brand name vs generic drug prescription.

d. Generic/brand name

In this study medicines were considered generic if they were marketed with the INN of the active substance. In order to evaluate the rate of recurrent prescriptions associated with the use of generic/brand name formulations, a list of the most used antibiotics with generic formulations was identified. Only antibiotics with paediatric generic formulations that had been marketed for more than two years were selected (for which a consolidated use is likely): amoxicillin, amoxicillin clavulanate, clarithromycin, and cefaclor. For each active substance, for both generic and brand name formulations, and for each age strata, the percentage of recurrent prescriptions was calculated.

e. Hospital admissions

In order to test if a generic or a brand name drug was prescribed, data concerning hospital admission were linked with the index prescription occurring in the observational period in the same patient. To test this hypothesis, data from hospital discharge records, including information on primary diagnoses and up to five coexisting conditions, procedures performed and dates of admission and discharge, were retrieved. The diagnoses were categorised according to ICD9 (International Statistical Classification of Diseases and Related Health Problems). Only primary diagnoses were considered. Hospital admissions occurring in the first week of life were excluded and/or those corresponding to the following diagnoses: tumors (ICD9 from 140 to 239), epilepsy (343-345), appendicitis (540-

543), hernia of abdominal cavity (550-553), complications of pregnancy, childbirth, and the puerperium (630-677), congenital anomalies (740-759), conditions originating in the perinatal period (760-779), and injury and poisoning (800-999). Children/adolescents having more than four hospital admissions in the considered period were excluded. For each active substance, for both generic and brand name formulations, and for each age strata, the percentage of patients with a hospital admission within 28 days following a prescription was calculated. Only children with at maximum 4 antibiotic prescriptions and 4 hospital admissions in the 6 months period were considered for this analyses, because it was very complicated to evaluate the different time-windows between more than 8 events in 6 months per each child.

f. Statistical analysis

Children/adolescents were divided into three age strata: 0-5, 6-11, and 12-17 years old. χ^2 was used to compare the two main outcomes (percentage of recurrent prescriptions and rate of hospital admission) in each age strata in children receiving brand name and generic prescriptions. The Cochran–Mantel–Haenszel test was used to compare the main outcomes in children receiving brand name or generic prescriptions, taking into account the different distribution of events in the three age strata. Statistical analysis was performed using SAS software, version 9.2 (SAS, Cary, NC, USA).

3. Results

In 2010 702,673 children/adolescents (42.1% of the total) received 1,248,570 antibiotic prescriptions. During the observational period a total of 329,123 children/adolescents received 494,496 antibiotic prescriptions (42.0% of the annual prescriptions). The chosen period was representative of the whole antibiotic prescription profile registered during 2010. Of these children 5,246 were excluded because they received more than four prescriptions.

Amoxicillin clavulanate, amoxicillin, clarithromycin, cefaclor, azithromycin and cefixime were the most used antibiotics and covered 87% of the prescriptions. A total of 271,697 children (82.6% of the total) received at least one prescription of the four antibiotics having paediatric generic formulations, for a total of 381,720 prescriptions. Amoxicillin clavulanate was the most prescribed antibiotic covering 54.8% of these prescriptions, followed by amoxicillin (25.4%), clarithromycin (12.6%), and cefaclor (6.2%). The overall percentage of generic prescriptions was: 70.4% for amoxicillin, 40.5% for amoxicillin clavulanate, 35.0% for cefaclor, and 16.3% for clarithromycin.

a. Therapy switch

Considering the three most used classes of antibiotics, a therapy switch occurred in 38.1% of cases in which the index prescription involved a penicillin, in 55.5% of cases involving a cephalosporin, and in 57.5% involving macrolides. The percentage of therapy switches per active substance was lowest for amoxicillin clavulanate (46.7%) and highest for cefixime (72.1%). The most common recurrent prescriptions involved the same drug prescribed in the index prescription for all the active substances considered.

Table 16 – Number of prescriptions of the most used active substances and percentage of their recurrences (including therapy switches). The numbers in parentheses indicate the number of index prescriptions.

$R^1 \backslash I^2$	amoxiclav*	amoxicillin	clarithromycin	cefaclor	azithromycin	cefixime	other
	(%)	(%)	(%)	(%)	(%)	(%)	(%)
amoxiclav* (24839)	53.3	6.2	11.4	4.6	7.9	4.5	12.1
amoxicillin (12440)	25.9	40.7	10.3	5.5	6.2	3.7	7.7
clarithromycin (5579)	30.2	8.3	34.8	3.7	6.8	4.4	11.8
cefaclor (3125)	23.9	7.4	9.1	39.6	9.1	3.7	7.2
azithromycin (3568)	28.6	7.7	9.0	3.9	34.9	5.2	10.7
cefixime (2605)	28.6	7.2	11.7	1.6	10.4	29.7	10.8

¹ recurrent prescriptions

² index prescriptions

* amoxicillin clavulanate

When a therapy switch occurred, amoxicillin clavulanate was the most used active substance in the recurrent prescription, Table 16.

The analysis on generic/brand name formulations concerned amoxicillin clavulanate, amoxicillin, clarithromycin and cefaclor, since for these drugs paediatric generic formulations had been available for at least two years, suggesting a consolidated use. During recurrent prescriptions the percentage of generic formulations used was substantially the same as that observed in the overall prescription sample. In cases in which a generic antibiotic was prescribed as the index prescription, a generic antibiotic was prescribed again in about half of the cases, ranging from 47.0% (clarithromycin) to 57.4% (cefaclor). When the same active substance was prescribed during a recurrence, there was a high percentage of same-type index-recurrent prescriptions (generic-generic and brand name- brand name). For generics the percentages ranged from 65.9% for clarithromycin to 93.6% for amoxicillin, and for brand names they ranged from 86.7% for amoxicillin to 96.2% for clarithromycin).

b. Generic/Brand name

The number and percentage of recurrent prescriptions for each of the four active substances, and for generic vs brand name formulations, is reported in Table 17.

Table 17 – Number and percentage of recurrent prescriptions among children receiving a generic or brand name formulation of the four antibiotics considered. The outcome in the two populations was evaluated through a χ^2 test. The significant odds ratios and confidence intervals are in bold.

	age	recurrent prescription				χ^2 (generic vs brand name)	
		generic formulation		brand name formulation		OR	95% CI
		N.	%	N.	%		
amoxicillin	0-5	6,732/45,597	14.8	1,769/11,615	15.2	0.96	0.80-1.16
	6-11	1,874/17,172	10.9	1,109/10,103	11.0	0.99	0.70-1.41
	12-17	358/4,338	8.3	598/6,563	9.1	0.90	0.33-2.48
	0-17	8,964/67,107	13.4	3,476/28,281	12.3	0.97*	0.91-1.02
amoxicillin	0-5	6,076/43,507	14.0	8,602/56,563	15.2	0.91	0.87-0.94
clavulanate	6-11	2,637/23,964	11.0	4,783/39,333	12.2	0.89	0.85-0.94
	12-17	1,004/10,186	9.9	1,737/16,587	10.5	0.94	0.86-1.02
	0-17	9,717/77,657	12.5	15,122/112,483	13.4	0.91*	0.87-0.94
cefaclor	0-5	832/5,193	16.0	1,328/8,515	15.6	1.03	0.94-1.14
	6-11	252/1,980	12.7	598/4,530	13.2	0.96	0.82-1.12
	12-17	29/196	14.8	96/820	11.7	1.31	0.84-2.05
	0-17	1,113/7369	15.1	2,022/13,865	14.5	1.02*	0.93-1.12
clarithromycin	0-5	340/2,118	16.1	2,265/16,150	14.0	1.17	1.04-1.33
	6-11	305/2,372	12.9	1,590/12,475	12.8	1.01	0.89-1.15
	12-17	285/2,750	10.4	794/7,736	10.3	1.01	0.88-1.16
	0-17	930/7,240	12.9	4,649/36,361	12.8	1.07*	0.96-1.19
overall	0-5	13,980/96,415	14.5	13,964/92,848	15.0	0.96	0.93-0.98
	6-11	5,068/45,488	11.1	8,080/66,441	12.1	0.91	0.87-0.94
	12-17	1,676/17,470	9.6	3,225/31,706	10.2	0.94	0.88-1.00
	0-17	20,724 / 159,373	13.0	25,269/190,995	13.2	0.96*	0.93-0.98

* Cochran–Mantel–Haenszel test, taking into account the different distribution among age-strata.

When considering the distribution of events among the three age-strata in the group receiving amoxicillin clavulanate, there was a slightly lower rate of recurrent prescriptions

in children receiving a generic formulation (OR 0.91; 95% CI 0.87-0.94). A similar, yet not clinically relevant, result was observed when comparing the children receiving any generic or brand name antibiotic (OR 0.96; 95% CI 0.93-0.98).

c. Hospital Admission

A total of 3,469 hospital admission occurred within 28 days from an index prescription during the observational period. Of these 3,077 (88.7%) occurred in children receiving one of the four selected antibiotics. The percentage of overall hospital admissions occurring in children treated (as index prescription) with a brand name (1.01%; 95% CI 0.98-1.08%) or a generic drug (1.03%; 95% CI 0.96-1.06%) did not differ ($\chi^2=0.543$; $p=0.43$). The number and percentage of hospital admissions for each of the four active substances and for generic vs brand name formulations is reported in Table 18. When adjusting for events occurring in the three different age strata (Cochran–Mantel–Haenszel test), the OR was significant (0.86; 95% CI 0.76-0.96) for amoxicillin clavulanate, with a lower percentage of hospital admission in patients receiving a generic formulation compared with those receiving a brand name one ($p=0.002$), Table 18.

When using a composite endpoint (the percentage of children with either a hospital admission or a recurrent prescription in both generic and brand name groups) the results were similar to those already observed.

Table 18 – Number and percentage of hospital admissions among children receiving a generic or brand name formulation of the four antibiotics considered. The outcome in the two populations was evaluated through a χ^2 test. The significant odds ratios and confidence intervals are in bold.

	age	hospital admission				χ^2 (generic vs brand name)	
		generic formulation		brand name formulation		OR	95% CI
		N.	%	N.	%		
amoxicillin	0-5	556/39,931	1.39	132/10,475	1.26	1.11	0.91-1.34
	6-11	79/13,872	0.57	40/8,860	0.45	1.26	0.86-1.85
	12-17	27/4,041	0.67	28/6,168	0.45	1.48	0.87-2.51
	0-17	662/57,844	1.14	200/25,503	0.78	1.16*	0.96-1.41
amoxicillin	0-5	443/35,754	1.24	688/46,043	1.49	0.83	0.73-0.93
clavulanate	6-11	122/19,690	0.62	231/32,280	0.72	0.87	0.69-1.08
	12-17	75/9,456	0.79	118/15,184	0.78	1.02	0.76-1.37
	0-17	640/64,900	0.99	1,037/93,507	1.11	0.86*	0.76-0.96
cefaclor	0-5	49/4,784	1.02	81/7,800	1.04	0.99	0.69-1.41
	6-11	9/1,756	0.51	14/4,030	0.35	1.48	0.64-3.42
	12-17	1/170	0.59	3/707	0.42	1.39	0.14-13.4
	0-17	59/6,710	0.88	98/12,537	0.78	1.05*	0.74-1.50
clarithromycin	0-5	26/2,109	1.23	224/15,544	1.44	0.85	0.56-1.28
	6-11	10/2,262	0.44	74/11,499	0.64	0.69	0.35-1.32
	12-17	13/2,622	0.50	34/7,171	0.47	1.05	0.55-1.99
	0-17	49/6,993	0.70	332/34,214	0.97	0.85*	0.57-1.26
overall	0-5	1,074/82,578	1.30	1,125/79,862	1.41	0.92	0.85-1.00
	6-11	220/37,580	0.59	359/56,669	0.63	0.92	0.78-1.09
	12-17	116/16,289	0.71	183/29,230	0.63	1.14	0.90-1.44
	0-17	1,410/136,447	1.03	1,667/165,761	1.01	0.94*	0.87-1.02

* Cochran–Mantel–Haenszel test, taking into account the different distribution among age-strata.

4. Discussion

To the best of our knowledge this is the first pharmacoepidemiological study using a database of health determinants to compare generic and brand name antibiotic recurrences in children and adolescents.

The findings did not show any substantial differences in the percentage of recurrent prescriptions in children receiving a generic or a brand name formulation when looking both at the overall antibiotic prescriptions and the single active substances. In fact, when looking at specific active substances and age-strata there are statistically significant differences, but when adjusting for age the differences observed disappear. In the case of amoxicillin clavulanate the prescription of a brand name formulation seems to be associated with slightly higher rates of both recurrent prescriptions and hospital admissions. Nevertheless, the absolute differences observed are very small, and not clinically significant. In fact, statistical significance is due to a very large sample size, especially for the amoxicillin clavulanate group, and, consequently, very narrow confidence intervals. Moreover, it is not possible to exclude the presence of susceptibility bias, occurring when the treatment regimen selected for a patient depends on the severity of the patient's condition. In fact if physicians were, at least in part, biased toward the prescription of a generic, they could have more often prescribed the brand name amoxicillin clavulanate to patients with the more severe disease at presentation. The considerations above are valid also for the group of children receiving any generic antibiotic compared to those receiving any brand name antibiotic.

When taking into account the distribution by age, the number of recurrences and hospital admissions were not higher in the generic drug group for any of the antibiotics considered, highlighting the fact that children exposed to generics do not appear to be more prone to recurrences. The findings are consistent with efficacy outcomes evaluated in previous clinical trials involving brand name and generic antibiotic formulations [155,156]. In the literature very scant data are available concerning the effectiveness of generic and brand

name antibiotic formulations in the outpatient setting. In fact, most studies evaluated effectiveness in hospitalised patients, involving carbapenems or piperacillin/tazobactam [155, 159-161].

The general prescription profile is the same observed in other pharmacoepidemiological studies that reported data about the same setting and population of patients [20,145]. When a recurrence occurred, the same active substance was prescribed again in most cases. This finding is not surprising and probably implies that, in most cases, physicians were convinced that a longer therapy with the same antibiotic would have been successful. Concerning therapy switches, the findings highlighted the fact that amoxicillin clavulanate was the most used antibiotic when a recurrence occurred, independently of the active substance used as the index prescription. In these cases physicians might be convinced that the previous antibiotic course failure was due to beta-lactamase producing bacteria (when amoxicillin alone was given).

In about half of the cases, children receiving a generic drug during the index prescription switched to a brand name formulation when a recurrence occurred: this fact may be due, at least in part, to the switch in active substance. In fact, different antibiotics have different rate

s of generic use, e.g. the amoxicillin clavulanate generic prescription rate is lower than that of amoxicillin. On the contrary, when physicians prescribed the same active substance in the recurrence, there was a high concordance of use of generic and brand name formulations in the index and recurring prescriptions. It would seem therefore that physicians tend not to change their prescribing attitude when the same antibiotic is chosen. In Italy generic drug prevalence is particularly low compared to the rest of Europe, with less than one in three antibiotic prescriptions constituted by generic formulations in the Lombardy Region, and the percentage is likely to be lower in other regions [162]. Patients' opinions on generic drugs can influence the likelihood of receiving a generic prescription, but if their doctor is willing to explain why generic drugs are as effective as the brand name

ones the rate of acceptance of drug substitution rises [163]. Unfortunately, in daily clinical practice, the physician's main source of information about drugs are pharmaceutical company representatives, and these representatives can greatly influence their perception about generic drugs [164]. The literature reports that a significant proportion of physicians, especially the older ones, have negative perceptions of generic drugs [164], and this is probably the most relevant deterrent to generic prescriptions, also in Italy [137]. Our findings are in agreement with most of the literature on generic antibiotics, which states that they are a safe [149,156] and economic alternative [22,149] to brand name ones. Despite these facts generic formulations continue to be underused, and the reason is likely to be biased information on generic drugs [137]. Although the cost analysis of generic vs brand name antibiotics was not the goal of the present study, the use of generic antibiotics (also in children) is cost-effective [22, 162].

In order to promote a more rational and cost-effective drug use, new approaches to physicians' education and information about drugs should be undertaken by policy makers, promoting a more correct and less biased vision of the generic market among physicians.

5. Strengths and Limits

This study included a large cohort of children/adolescents, retrospectively followed for 3 months, including all the reimbursed prescriptions filled by FPs and GPs. The cohort of children/adolescents included the total population of a large Italian region, avoiding possible selection biases derived from different socio-economic and cultural backgrounds. Hospital admissions and composite endpoint analyses were included as a proxy of severe disease and therapy failure, showing results in complete agreement with those observed during the recurrent prescription analysis.

Some intrinsic limitations are present given that this is a retrospective observational study. A recurrent prescription within 28 days of an index prescription is used in this study as a

proxy of therapy failure, and although this is a quite arbitrary period, this approach was already used in literature [165]. When looking at recurrent prescriptions, it is possible that some were actually relapses (second infection with the same organism) or reinfections (different organism), and we were not able to discriminate between them. The previously described susceptibility bias could have been adjusted only by knowing the diagnosis and the clinical anamnesis, which was not the case. Despite this, it is likely that the diseases, including a number of non-recognized viral infections, were distributed evenly between the groups of patients receiving a generic or brand name antibiotic, so the results should not be influenced.

Only antibiotics with paediatric generic formulations marketed for more than two years were included in this study (amoxicillin, amoxicillin clavulanate, clarithromycin, and cefaclor). The four drugs covered 87% of the overall antibiotic prescriptions, the use of other generic antibiotics was uncommon, and the comparison with the group receiving the brand name alternatives not feasible. We also could not ascertain compliance to treatment or if the drug was actually consumed by patients: these are limitations common to all pharmacoepidemiology studies using prescription databases.

6. Conclusions

Findings showed that children initially treated with a generic formulation of the considered antibiotics had no different safety and effectiveness outcomes compared to those treated with a brand name formulation. The results of the study are in agreement with most of the literature on this topic and provide additional evidence on the safety of use of generic antibiotics in the outpatient setting, an area that is scanty investigated. The anecdotal reports of non-effectiveness are not justified by the data observed in this study and may be due to economic interests more than real differences. Policy makers should promote

objective information on generic drug use in order to hinder the pressure to prescribe a brand name formulation exerted by pharmaceutical representatives on physicians.

Finally, even if with a few limitations, this study supports the usefulness of routinely acquired healthcare data in terms of clinical research potential, even if these results should be validated against a gold standard.

D. Assessing the quality of paediatric antibiotic prescribing by community paediatricians: a database analysis of prescribing in Lombardy

1. Introduction

The lack of appropriate use of antibiotics and antibiotic resistance have been worldwide problems for the last few decades [166]. Unnecessary antibiotic prescriptions for viral diseases, and the use of second choice therapies for certain conditions, can increase antibiotic resistance also in the community setting (i.e. *S.Pneumoniae* resistance to macrolides) [166,167]. Since children are among the most exposed to this drug class, rational antibiotic prescribing in paediatrics is of paramount importance [1].

Antibiotics are overused in outpatient children in Italy more often compared to other European countries [4]. Frequent prescriptions of second choice treatments, and wide heterogeneity in prevalence at different geographic area levels (34.0 to 67.9 % among healthcare districts) have been identified and described [6,12,122]. Amoxicillin is the first line treatment for respiratory infections in children in the community setting, and we previously used it as a proxy of appropriateness in Italy ,with large differences in prevalence ranging from 8.7% to 28.1% among regions, and from 7.1 to 48.0% among local health units [6,168]. The percentage of children treated with amoxicillin was later proposed as an indicator of the quality of prescribing (amoxicillin index) by de Bie et al [169].

The FP's prescribing attitude has already been identified as one of the main determinants of differences in antibiotic prevalence at the area level [12]. Despite this, the association between the amount of antibiotics prescribed and the qualitative profile is a scantily studied topic. Moreover most epidemiological studies on drug prescription patterns are based on administrative databases that rarely contain the indication for the prescription. Thus, evaluating appropriateness on a selected population by developing specific quality indicators may be a useful proxy for the quality of antibiotic prescribing.

The aim of this study was to evaluate the quality of FPs' antibiotic prescribing through administrative databases by analysing a selected population of children and by using indicators at the population level.

2. Methods

a. Data source

The data source was the database of the Lombardy Region, which is routinely updated for administrative and reimbursement reasons. The region is divided into 8 Local Health Units, which are further divided into two to seven smaller areas called ASSTs (Social health territorial units), for a total of 27 ASST. The three ASSTs referring to the city of Milan are considered as a unique ASST in this study. Only drugs reimbursed by the NHS are included in the database. Anonymous data were provided by the regional health ministry of the Lombardy Region. All drugs were classified according to the ATC system (Anatomical Therapeutic Chemical classification system).

b. Index prescription

An index prescription was defined as the first antibiotic prescription in 2011 that occurred without: an antibiotic prescription in the previous 60 days, a hospital admission in the previous 60 days, and an emergency department admission in the previous 14 days.

c. Inclusion criteria

Children and adolescents 1-13 years old, cared for a FP, who received at least one index prescription during 2011 were included.

d. Exclusion criteria

Children who received 7 or more antibiotic prescriptions (95th percentile of the distribution of annual prescriptions per children at four years of age, the age with the most antibiotic prescriptions) in the 365 days either before or after the index prescription were excluded (31,899; 2.7% of the resident population). This criteria ensured that children included in the

study were not patients with chronic infections, or with other conditions requiring recurrent antibiotic courses.

Children who were not residents in the Lombardy Region from the year before the index prescription until the end of the follow up period were excluded. Children in the first year of life were excluded because of possible treatments for bronchiolitis.

Children who were residents in one of two specific ASSTs were excluded because data on emergency department admissions were not available.

Children who were not cared for by a FP were excluded (59,875; 5.0% of the resident population), and those who were cared for by FPs with less than 98 patients (10° percentile of the distribution of the number of children per FP) were excluded in order to have a more homogeneous population of FPs (1,760 patients; 0.1%).

Of the 1,002,006 resident children, 424,280 (cared for by 1,164 FPs) satisfied the inclusion and exclusion criteria and were included in the study.

e. Measures

The percentage distribution of antibiotic prescriptions by class and active substance (for amoxicillin and amoxicillin clavulanate) was investigated.

f. Data analyses

Each child or adolescent, and FP, was followed for one year from the index prescription.

The profile of antibiotic prescriptions was estimated at the population level:

- 1) at the index prescription;
- 2) in unrelated infective episodes, identified by a new antibiotic prescription occurring 30 days or more after the index prescription.

g. Quality indicators

- The A indicator was the proportion of children who received amoxicillin by the FP at the index prescription. From the prospective evaluation of data in paediatric ambulatory care in Italy it is known that more than half of the systemic antibiotics are prescribed for pharyngotonsillitis (26.9%) and acute otitis media (AOM; 24.4%) [170]. In case of bacterial

AOM and pharyngotonsillitis, amoxicillin is the first line therapy because, respectively, *S. Pyogenes* (always sensible)[171-173] and *S. Pneumoniae* (highly sensible in 90% of cases [171,174-177]) are the pathogens that are able to cause the most important complications. Amoxicillin is the first line therapy also in case of scarlet fever caused by *S. Pyogenes* (3% of antibiotic prescriptions [170]), uncomplicated pneumonia [178,179], and sinusitis [170,180]. Hence we estimated that at least 50% of patients treated with an antibiotic should be initially treated with amoxicillin (target for the A indicator).

- The B indicator was the proportion of children who received cephalosporins or macrolides, exclusively, by the FP for every unrelated infective episode. The maximum target percentage was set at 10%. The rationale of this criterion was that self-reported hypersensitivity to beta-lactams in children varies from 1.7 to 7.9% [181-183]. We are therefore confident that in no more than 10% of children hypersensitivity can justify the exclusive prescription of second choice treatments throughout the year.

Number of FPs that reached the target for the A or B indicators has been estimated also at the ASST level. Number of FPs that reached the target for both indicators was also estimated.

The geographical distribution of FPs in respect to the quality indicators was represented in choropletic maps. Clusters and outlier values were calculated by using the Anselin Local Moran's I statistic [184].

The FPs were categorised based on the distribution of the average number of antibiotic prescriptions per patient, considering all their patients ≥ 1 to 13 years old: low prescriber corresponded to the arithmetical mean minus the standard deviation ($y < \bar{x} - sd$, lower than 0.74), a mean prescriber to $\bar{x} - sd < y < \bar{x} + sd$ (0.74 to 1.44), and high prescriber to $y > \bar{x} + sd$ (higher than 1.44). The same criteria were used for classifying FPs in respect to age (young ≤ 44 ; adult 45-59; and elderly ≥ 60), and in respect to number of patients (low ≤ 645 ; mean 646-1,076; and high $\geq 1,077$). The quality of prescription (A and B indicators) was estimated in the different groups of FPs (low/mean/high prescriber). Cochran-Mantel-

Haenszel test for trend was used to test the difference among low, mean, and high prescribers. A multivariable logistic regression analysis was performed at the FP level on the likelihood of reaching the target for both A and B indicators. The FPs' covariates considered were: sex, age, prescribing pattern in respect to quantity of antibiotic prescriptions, number of children cared for by each FP, and area of residence. The variables entered the model by a stepwise selection with a significance $\alpha=0.05$.

The statistical analyses were performed with SAS 9.5, and the cartographic representations and spatial analyses with ArcMap 10.5.

3. Results

Of the 1,002,006 children 1 to 13 years old in our sample, 49.9% received at least an antibiotic prescription. Prevalence decreased with increasing age from 63.9% (1 to 5 years old) to 30.4% (10 to 12 years old).

Overall 1,164 FPs cared for a median of 857 children (IQR 736-1012). FPs were mostly females (75.3%), and the median age was 53 years old (IQR 48-56).

a. Prescription profile

Of the 424,280 children included in the study with an index prescription: 146,582 (34.5%) received one antibiotic prescription, 115,541 (27.2%) received two prescriptions, and 162,157 (38.2%) received three to six prescriptions in the year of follow-up. Penicillins were prescribed in 68.6%, macrolides in 16.5% and cephalosporins in 13.3% of cases at the index prescription. The most prescribed active substance was amoxicillin clavulanate at any age, table 19.

Table 19 – Percentage distribution of children at the index prescription by active substance and age strata

	≥1 year		2-5 years		6-9 years		10-13 years		Total	
	n	%	n	%	n	%	n	%	n	%
amoxicillin clavulanate	25,858	41.1	91,630	46.0	51,146	46.3	21,699	42.2	190,333	44.9
amoxicillin	22,350	35.5	46,730	23.4	21,789	19.7	9,696	18.9	100,565	23.7
clarithromycin	3,286	5.2	15,838	7.9	11,136	10.1	6,581	12.8	36,841	8.7
azithromycin	2,577	4.1	13,835	6.9	9,885	8.9	6,298	12.3	32,595	7.7
cefixime	2,499	4.0	8,765	4.4	4,816	4.4	2,368	4.6	18,448	4.3
cefaclor	2,917	4.6	9,087	4.6	3,602	3.3	817	1.6	16,423	3.9
cefprozime	1,772	2.8	6,797	3.4	3,863	3.5	1,572	3.1	14,004	3.3
ceftibuten	836	1.3	2,595	1.3	1,237	1.1	423	0.8	5,091	1.2
fosfomicin	47	0.1	862	0.4	837	0.8	389	0.8	2,135	0.5
cefuroxime	195	0.3	782	0.4	531	0.5	311	0.6	1,819	0.4
other	291	0.5	1,087	0.5	786	0.7	711	1.4	2,875	0.7
> one antibiotic	293	0.5	1,392	0.7	951	0.9	515	1.0	3,151	0.7
Total	62,921	100	199,400	100	110,579	100	51,380	100	424,280	100

Amoxicillin was prescribed at the index prescription to 23.6% of children, this indicator varied widely at the area level ranging from 7.9% to 46.3% among ASSTs. In none of the ASST the percentage of children receiving amoxicillin at the index prescription reached the target of the 50%.

A total of 258,681 children (61.0%) had one or more unrelated infection episodes 30 days or more after the index prescription. The majority of these children (208,768; 80.2%) received different antibiotics during the year; 12.1% of children (31,192) received exclusively second choice treatments like macrolides and cephalosporins, and 7.7% (19,914) exclusively amoxicillin. These percentages varied widely between ASSTs: from 8.2% to 22.0% for the former indicator, and from 1.4% to 21.8% for the latter.

b. Paediatricians

Each FP prescribed amoxicillin at the index prescription to a median of 21.1% (IQR 9%-37%) of patients, and prescribed only non-penicillin antibiotics in unrelated infective episodes to 9.3% (IQR 6%-14%) of patients.

The percentage of FPs who reached the target of having prescribed amoxicillin at the index prescription to at least 50% of patients (A indicator) was 12.8%. The percentage of FPs who reached the target of having prescribed exclusively non-penicillin antibiotics in unrelated infection episodes to less than 10% of patients (B indicator), was 54.0%. Overall, 131 FPs (11.3%) reached the target for both indicators (covering 11.2% of the regional child population). On the contrary, 518 FPs (44.5%, covering 44.8% of the regional child population) showed inadequate quality of antibiotic prescribing, not reaching the target for either of the two indicators.

Table 20 - Distribution of two quality indicators among the FPs ordered by type of prescriber

Type of FP	Indicator A ¹				Indicator B ²				Adequate quality according to adherence to both indicators			
	No	Yes	Total	% Yes	No	Yes	Total	% Yes	No	Yes	Total	% Yes
Low prescriber	121	30	151	19.9	43	108	151	71.5	122	29	151	19.2
Mean prescriber	751	107	858	12.5	395	463	858	54.0	765	93	858	10.8
High prescriber	143	12	155	7.7	98	57	155	36.8	146	9	155	5.8
Total	1,015	149	1,164	12.8	536	628	1,164	54.0	1033	131	1,164	11.3
p³	0.002				<0.001				<0.001			

1. FPs who prescribed amoxicillin at the index prescription to at least 50% of their patients
2. FPs who prescribed only non-penicillin antibiotics in unrelated infective episodes to a maximum of 10% of their patients included in the study.
3. Cochran-Armitage trend test

High prescribers were less likely to prescribe amoxicillin at the index prescription (χ^2 for trend $p=0.002$), and were more likely to prescribe only non-penicillin antibiotics (χ^2 for trend $p<0.001$), table 20. The univariable analysis showed that FPs with an adequate quality of antibiotic prescribing (reaching the target for both the A and B indicators) were more likely to be: low prescribers, males, elderly, and resident in a specific cluster of high values identified by the spatial analyses in a urban area in north of Milan, figure 6 and table 21.

Figure 6 - Distribution of the FPs that prescribed amoxicillin alone at the index prescription to at least 50% of their patients included in the study (A indicator), and of the percentage of FPs that prescribed exclusively non-penicillin antibiotics in different infection episodes to more than 10% of their patients included in the study (B indicator). Spatial cluster analysis of the distribution of the indicators by ASST.

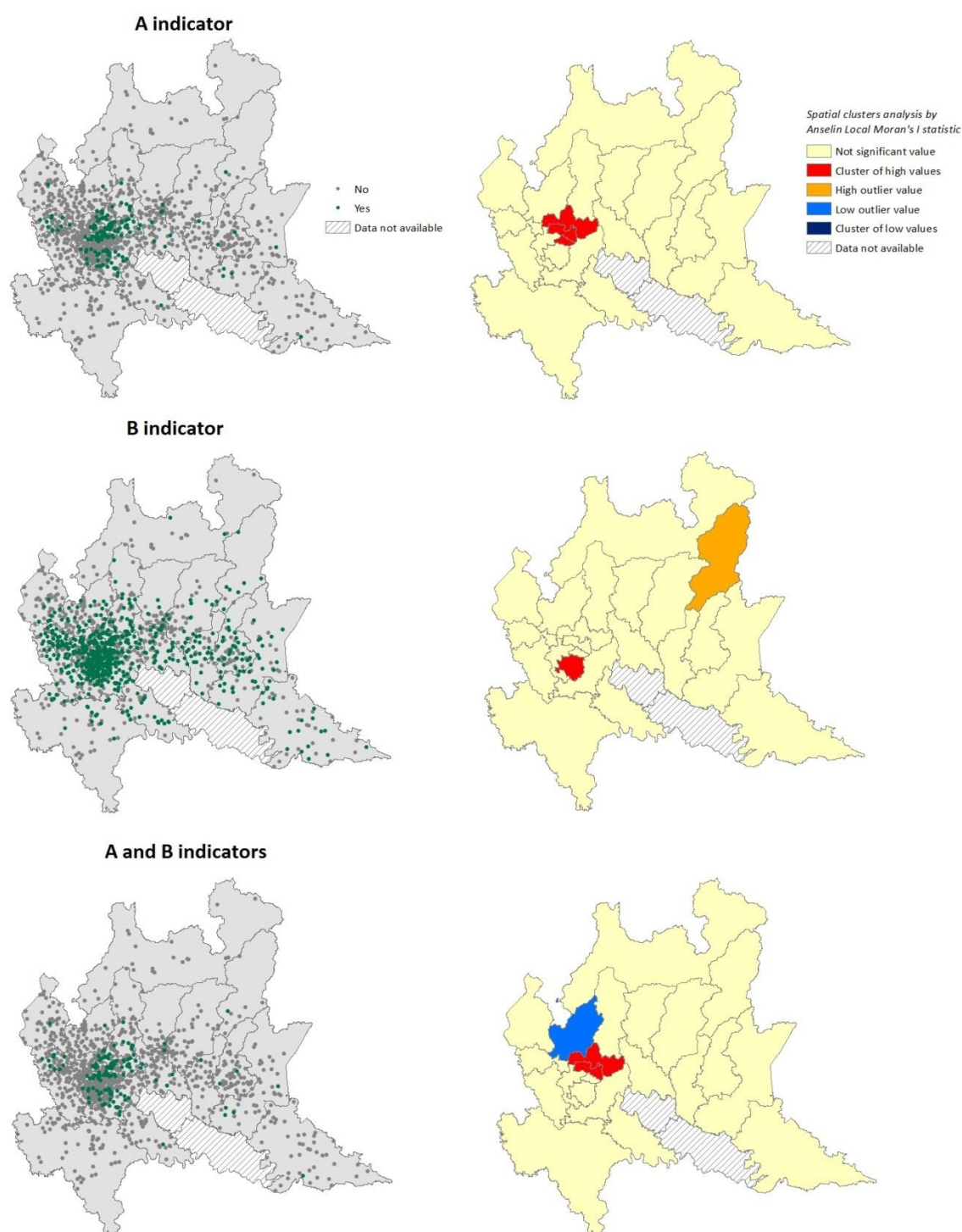


Table 21 – FPs characteristics and their association with reaching the target for both the A and B quality indicators (adequate quality).

FPs characteristics		FPs (%) adequate quality ¹	p ²
type of prescriber	low prescriber	19.2	<0.001
	mean prescriber	10.8	
	high prescriber	5.8	
sex	female	9.8	<0.001
	male	15.6	
age (years)	≤44	4.7	<0.001
	45-59	11.4	
	≥60	17.0	
number of patients	low ≤645	8.2	0.031
	mean 646-1,076	12.9	
	high ≥1,077	7.1	
area of residence	urban area at north of Milan ³	39.5	<0.001
	other areas of the region	8.2	

1. FPs that reached the target for the A and B quality indicators
2. χ^2 test
3. this area includes those that are part of the cluster identified in Figure 6

At the geographic level there was a huge variability in quality of prescribing, with a percentage of FPs who reached the target for the A indicator ranging from 0 to 53.0%, and for the B indicator ranging from 9.1 to 84.8% between ASSTs, figure 6. In three ASSTs no FP reached the targets, and only in one ASST more than 50% of FPs did.

The multivariable analysis showed that the FP determinants of adequate quality of antibiotic prescribing were the geographic factor, being a low prescriber, and being elderly, table 4. Sex and the number of patients were not relevant factors in the multivariable model, and were excluded by the stepwise selection of covariates.

Table 22 – Logistic multivariable regression model for the likelihood of each FP of reaching the target for both the A and B quality indicators according to sex, age, prescribing pattern in respect to quantity of antibiotic prescriptions, number of children cared for by each FP, and area covered by FPs' offices.

Covariates		OR ¹	CI 95%
type of prescriber	low prescriber	4.61	(1.99 – 10.69)
	mean prescriber	2.26	(1.08 – 4.75)
	high prescriber	1.00	-
age (years)	≤44	1.00	
	45-59	2.41	(1.07 – 5.46)
	≥60	3.98	(1.58 – 10.04)
area covered by FPs' offices	urban area at north of Milan ²	8.64	(5.47 – 13.66)
	other areas of the region	1.00	-

1. sex and number of children cared for by each FP did not enter the model according to the stepwise selection
2. cluster of high values identified in Figure 6, according to the Anselin Local Moran's I statistic

4. Discussion

To the best of our knowledge this is the first study evaluating the quality of FPs' antibiotic prescribing through an administrative database in Italy.

In order to reach our objective, we selected, and monitored, children who were receiving a course of treatment not preceded by any antibiotic prescription and/or hospitalization in the preceding two months. In this regard, we were confident that, at least for the index prescription, amoxicillin would be prescribed to the majority of children in our sample. At the population level this was not found, and only 24% of children (less than half of expected) received amoxicillin as the index prescription. Despite the fact that the Lombardy Region is among the settings with a relatively low antibiotic prescription rate in Italy, the above findings reveal a poor average quality of prescriptions.

In other international studies the amoxicillin index was found to be very heterogeneous [4,169,185,186], ranging from 21.1% in Germany to 46.8% in the Netherlands, even if in Germany phenoxymethylpenicillin appropriately accounts for a significant additional

proportion of prescriptions, differently from Italy. First line penicillins were found to be scantily prescribed in Italy in a recent study comparing 6 different countries: from 64.8% of antibiotic prescriptions in Norway, to 24.1% in the Pédianet database (Italy) and 8% in the Lazio Region (Italy) [187]. We were not able to find studies that evaluated the FPs' quality of prescribing at the prescriber level with criteria comparable to those used in our study. Only one French study investigated the qualitative profile of community paediatricians at the prescriber level, finding cefpodoxime as the most prescribed antibiotic, and amoxicillin representing 25% of the antibiotic prescriptions [188]. Other studies evaluated the appropriateness of antibiotic prescribing at the population level or comparing different type of prescriber [189,190]. In these studies the first-choice antibiotics were prescribed in 50%-85% of episodes, and there were wide qualitative differences among GPs and FPs [189,190].

In our study the most prescribed antibiotic was amoxicillin-clavulanate at any age, even though it is less palatable and tolerable than amoxicillin alone [191,192]. It is very likely that this happens for fear of infections caused by beta-lactamase producing bacteria. This is unjustified by the evidence, which shows that beta lactamase producing bacteria in AOM or sinusitis, for example, are those causing less severe complications and whose infections most commonly resolve spontaneously [174,176,180].

Different factors (e.g poor education, parental expectation of a prescription), may explain some of the qualitative and quantitative differences between Italy and other countries. It is likely that most of the differences observed in our study are due to the FPs' prescribing patterns. We already documented that in the areas where antibiotic prevalence is higher, high prescribing FPs are more frequent [12]. In this regard, the current study adds relevant findings concerning quality of prescriptions.

The percentage of FPs with adequate quality of antibiotic prescribing was extremely low, and almost half of the FPs did not reach the target for both the A and B indicators. This means that almost half of the regional child population was treated with antibiotics that

exposed them to greater potential risks. An impressive variability was found between ASSTs, with only one having more than 50% of FPs with good quality prescribing, and three ASSTs with no FPs reaching the target. It is quite striking that there were a few FPs who did not prescribe the recommended treatment at all at the index prescription to any of their patients.

When looking at the percentage of children receiving second line treatments only (macrolides and/or cephalosporins, B indicator) in all the infection episodes, the average value was slightly above the threshold expected on the basis of the frequency of beta-lactams hypersensitivity. Also in this case a huge variability was found between ASSTs, with some geographical settings exceeding 20%. Cephalosporins are hardly ever prescribed in the community setting in most of the north European countries and do not present significant benefits over amoxicillin in most cases [4]. Macrolides are very susceptible to developing resistance, and should be used in selected cases, or in hypersensitive patients [193].

Quantity of antibiotics prescribed was associated with quality. The proportion of FPs reaching the target for both indicators was almost fourfold higher in the low prescribing group compared to the high prescribing group. Considering, as an additional criteria of “good practice”, the limited prescription of antibiotics, only 29 out of 1164 FPs satisfied both A and B indicators and were also “low prescribers”. Additionally 146 out of 1164 FPs (12,5%) were high prescribers and did not reach the target for the quality indicators. Moreover, the Lombardy Region is among the regions with the highest amoxicillin index in Italy, it is thus expected that in other regions the quality indicators at the FP level will be worse [4].

The study highlighted a specific cluster of higher quality antibiotic prescriptions in an urban area slightly north of Milan. This confirms a long term effect of a continuous educational intervention (in the period 2004-2008) on a group of FPs in this area that was aimed at enforcing the international guidelines for antibiotic treatment of respiratory infections in

clinical practice [12,22]. The educational intervention was mainly based on peer comparison. The notable persistence is quite remarkable, and is different from the results that are usually obtained with educational interventions that are limited in time [194].

Other factors may be associated with the quality of prescribing, for example socio-economic factors. We already showed in a multiregional study that antibiotic prevalence is higher in low income areas [122]. We compared the amoxicillin index at the ASST level to the average annual income per resident, and found that the qualitative profile was likely to be worse in low income areas (not shown). However, since the Italian NHS is universalistic, being poor or wealthy is unlikely to influence the type of antibiotic prescribed, because parents of children don't have to spend money for antibiotics. Income deprivation in this case may be a proxy of cultural deprivation [67]. This correlation should be investigated also in countries with private health services. However we believe that prescribing attitude is the most crucial factor in the heterogeneity found because, even when looking at the same homogenous geographic context, FPs had very different qualitative profiles of prescribing. Finally, increasing paediatrician age was one of the factors significantly associated with a better quality of antibiotic prescribing. This finding is unexpected, since most studies on the association between quality of care and physician age were inconclusive or showed that older physician may be at risk of providing lower quality of care [190,195,196]. This is an important indication of the need for targeting educational interventions especially at the youngest FPs.

The main weakness of the study is the lack of the diagnoses. We, therefore, were not able to evaluate the appropriateness of prescriptions. Nevertheless, real world data concerning the access to primary care ambulatories for respiratory infections were used to identify the cut-offs for the quality indicators. We were able to analyse only reimbursed prescriptions, and not private practice paediatricians. However this fact has a negligible influence on the study, since the aim was to investigate the FPs' quality of antibiotic prescribing. The strength of the study is the possibility to compare the results with previous studies in the

overall paediatric population in the same region, and to establish the added value of this approach. The results showed that the quality indicators proposed, if further validated, may be a promising tool for benchmarking the antibiotic prescribing trend at the paediatrician level even without knowledge of the diagnoses, and could highlight those prescribing behaviours that deviate from the guideline indications.

5. Conclusions

The quality indicators proposed were able to identify areas of the region, and FPs, with inadequate quality of prescriptions. The youngest FPs and those who were not exposed to educational interventions showed a significantly worse quality of prescribing.

FPs who were part of a continuous educational programme on the improvement of antibiotic prescribing had a better prescription profile. After further validation, these quality indicators could be a surrogate benchmarking tool for comparing the quality of FPs' antibiotic prescriptions, when the diagnosis is unknown, in different settings.

VII. Overall discussion and conclusions

A. Summary

Quantitative and qualitative differences were found in drug prescribing in children and adolescents between regions and LHUs. Despite the differences, a prescribing profile specific to Italy was observed in all the settings, characterised by extensive use of antibiotic and anti-asthmatic drugs, and limited use of psychotropic drugs compared to other countries. The differences appear to be mainly related to prescribing attitudes in Italian physicians but also to other cultural factors and related to the population income.

B. Determinants and relevance

The geographical factor was one of the main determinants of antibiotic and anti-asthmatic drug prevalence. In particular, both lower latitude and income were associated with an higher prevalence of antibiotic and anti-asthmatic prescription, but not psychotropic drug prescription.

As we know, income in Italy is associated with latitude, i.e. in the South income is lower. However these drugs are fully reimbursed by the NHS, so the reason for this association is unlikely to be poverty. It is likely that these two factors may be a proxy for other socio-economic indicators such as educational deprivation, which is known to be higher in the South of the country. However it is very likely that the true cause of the association between the increased prevalence in these areas is still unknown since these are ecological studies with no individual level data, and a limited amount of covariates available.

The study on psychotropic drug prescription is the largest ever conducted in Italy. Psychotropic drug prescription in paediatric patients is a quite rare event, also strictly regulated in the case of ADHD drugs. It is likely that the closed surveillance and monitoring, and the need of a more specific disease knowledge for a parent whose child is in need for a psychotropic drug, may result in less interference with the physician's decision of a pharmacological treatment. This phenomena may mitigate differences among regions.

The research area on the quality of drug prescription, including generic drugs, the study about proxies of clinical effectiveness of generic versus brand name antibiotics, and the developing of the quality indicators at the paediatrician level is a quite innovative approach in this field. From the results of the studies the prescriber's attitude seems to be the main determinant of drug prescribing. The studies showed that high prescribing physicians tend to prescribe with a worse qualitative profile, by using less the first line antibiotic treatments, and by using more second choice treatments. They also tend to use less generic antibiotics. Also, conversely, we found that younger FPs prescribe less recommended treatments, and this is quite alarming.

The review of the literature was the first in this field. The review showed that there was indeed an association between parental and offspring drug prescription, at least for some kind of drugs, even considering socio-economic and educational confounders which may come into play. However the topic is scantily studied, and there is need for more studies in particular investigating the association among different drug classes. The hypothesis that some authors postulated concerning the possible role of parental stress, anxiety, and other kind of psychiatric conditions is quite interesting, and deserves ad hoc studies.

C. Possible priority interventions

The wide differences observed in terms of quality and quantity of prescriptions between and within regions suggest that educational interventions for health care professionals and parents may be effective in improving rational drug use. In particular more efforts are needed in certain geographical contexts characterised by a low prevalence, but associated with inappropriate drug use.

The findings from this thesis demand more attention and efforts by health policy makers in regards to:

- educational campaigns and local intervention to limit antibiotic prescriptions, especially in the South of Italy, but also in some particular areas of the North of the country;

- promoting the use of amoxicillin among FPs, that too often prefer amoxicillin clavulanate in Italy for fear of beta-lactamase producing bacteria, or other second line drugs such as cephalosporins and macrolides;
- promoting the use of rapid-antigen-detection tests (RADT) and other self-help instruments in paediatric ambulatory in order to reduce diagnostic uncertainty, which the literature shows to be among the most important factors determining the chance of an antibiotic prescription;
- progressively reducing, and eradicating, the widespread practice of non-evidence based treatments such as nebulised steroids for treating symptoms of URTI;
- promoting a working group on an acknowledged shared formulary in paediatrics, which could help in reducing the incredible number of redundant active substances that is currently used in the clinical practice;
- more standardised clinical and therapeutical approaches in the field of paediatric mental health among different geographic areas in the country, which could lead to a decreased use of off-label active substances in some cases, and an increased use of those treatments supported by more solid evidence;
- promoting generic drug prescription and use, through educational interventions to physicians and citizens stating that they are safe and effective alternatives to brand name drugs, and provide sustainability of the NHS;

Finally the studies described in this thesis confirm that pharmacoepidemiology is a valuable tool for monitoring drug prescribing and giving indications to policy makers. Merging different administrative databases (e.g. prescription, hospitalisation, specialist physician databases) may permit to observe determinants related to prescription attitudes.

D. Future perspectives

In order to overcome the limitations of administrative databases in the future, the study of the determinants of drug and other health resources use will continue by setting up a prospective birth cohort study. The birth cohort will evaluate the role of maternal and young child determinants on the health status during infancy and development. The cohort will collect a number of different information concerning birth, familiar characteristics and anthropometric information that cannot be obtained by administrative databases.

Finally, multinational collaborative studies are warranted, with the aim to collect representative and comparable data among different countries and different kind of health services, in order to improve the rational use of drugs and to guarantee safe and effective drug therapies to children and their families.

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